Medicines Adverse Reactions Committee

Meeting date	**14 September 2017**	Agenda item	3.2.1
Title	**Use of sodium valproate in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Sodium valproate	**Medicines** Epilim	**Sponsors** Sanofi	
Funding	Funded		
Previous MARC meetings	See Section 2.2		
International action	This issue is subject to an article referral in the EU, initiated on 9 March 2017, by the French Medicines Regulator		
Prescriber Update	www.medsafe.govt.nz/profs/PUArticles/Anticonvulsants-Feb09.htm www.medsafe.govt.nz/profs/PUArticles/June2013MedsInPregnancy.htm www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm		
Schedule	Prescription medicine		
Usage data	See section 4.1		
Advice sought	**The Committee is asked to advise whether:** – further regulatory action is required (eg, changes to the data sheet or indication) – further communication is required		

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1.0 PURPOSE

The purpose of this paper is to review the use of sodium valproate (Epilim) in pregnancy. The European Union (EU) is currently conducting an investigation into this issue. Therefore, it is timely to review the teratogenic and neurodevelopmental effects and investigate whether use in pregnancy has decreased since Medsafe issued reminders regarding this issue.

2.0 BACKGROUND

2.1 Sodium valproate

Sodium valproate (VPA), brand name Epilim, is a branched-chained fatty acid, which exerts its effects mainly on the central nervous system. Its main mechanism of action seems to be related to a reinforcement of the gamma-aminobutyric acid-ergic pathways.

The first international approval for valproate and related substances was obtained in France on 23 January 1967. Epilim was first approved in New Zealand in 1975.

Valproate and related substances are approved and marketed in more than 120 countries.

2.2 Previous MARC discussion

Since Epilim was approved the Medicines Adverse Reactions Committee (MARC) have reviewed many case reports of suspected adverse reactions including reports of teratogenic effects.

Sodium valproate and fetal abnormalities was a Watching Brief from December 2004. The Watching Brief was triggered by a Centre for Adverse Reactions Monitoring (CARM) report of a child born with probable fetal valproate syndrome and developmental delay. The mother had been started on valproate for the treatment of severe post-natal psychosis after her first child was born. Previous reports had occurred in mothers taking valproate for seizures and it had been argued that the fetal abnormalities might have been caused by seizures.

The MARC were provided with an update on the Watching Brief in December 2005. The MARC agreed that the issue could be removed from the Watching Brief. In December 2006, the MARC considered a further CARM report of fetal valproate syndrome and recommended that an article was included in *Prescriber Update*. The article was published in 2009.

In June 2009, the MARC considered a CARM report of twins who were diagnosed with fetal valproate syndrome at birth; the mother had been taking sodium valproate. The MARC noted that recent studies had been published showing that *in utero* exposure to valproate was associated with an increased risk of impaired cognitive function. The MARC recommended that the data sheet be reviewed. In November 2009, the MARC reviewed the information in the data sheet on use in pregnancy. The MARC recommended that the data sheet be updated to include information on cognitive impairment.

In 2015, the Committee MARC were presented with the text of the alert communication on use of sodium valproate in pregnancy.

2.3 Data sheets

The indications for sodium valproate (Epilim) are:

Epilepsy: Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy.

Bipolar Disorder: For the treatment of manic episodes, maintenance and prophylactic treatment of bipolar disease.

Epilim IV: The treatment of patients with epilepsy or bipolar disorder, who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Comments
In Europe, Epilim is only indicated for treatment of epilepsy. Valproate semisodium, brand name Depakote has the following indication: Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

Contraindications include:

Use of sodium valproate is contraindicated in pregnancy.

Warnings related to pregnancy:

Female children, female adolescents, women of child bearing potential and pregnant women:

This medicine should not be used in female children, in female adolescents, in women of child-bearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of this high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of child bearing potential treated with Epilim plans a pregnancy or if she becomes pregnant. This assessment is to be made before sodium valproate is prescribed for the first time, or when a woman of child bearing potential treated with sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated, and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses during pregnancy.

Women of child-bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy. The prescriber must ensure that the patient is provided with comprehensive information on the risks.

In particular the prescriber must ensure the patient understands

• The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.

• The need to use effective contraception.

• The need for regular review of treatment.

• The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to an appropriate alternate treatment prior to conception, if possible.

Epilim therapy should only be continued after a reassessment of the benefits and risks of the treatment with Epilim for the patient by a physician experienced in the management of epilepsy or bipolar disorder.

Use in Pregnancy (Category D)

Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of Epilim should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed.

Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, without reassessment of the risks and benefits, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. If after careful evaluation of the risks and benefits, sodium valproate treatment is to be continued during pregnancy, it is recommended to use sodium valproate in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.

In bipolar disorder, cessation of sodium valproate should be considered.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

In animals, teratogenic effects have been demonstrated in mice, rats and rabbits,

Congenital malformations:

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in children born to mothers treated with valproate, when compared to the incidence for certain other antiepileptic drugs. Data has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy. This is a greater risk of major malformations than for the general population. Women treated with Epilim IV have a potentially increased risk of giving birth to a baby with an abnormality due to the higher Cmax of the intravenous formulation compared with the oral formulation.

Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine. Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%. This risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Developmental disorders:

Data has shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that some children may experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Some data have suggested an association between in-utero valproate exposure and the risk of impaired cognitive function, including developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. IQ measured in school aged children with a history of valproate exposure in utero, was lower than those children exposed to other antiepileptics. Although

the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There is limited data on the long term outcomes.

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Autism spectrum disorders have also been reported in children exposed to valproate in-utero.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

In view of this data, the following recommendation should be taken into consideration:

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary, that is, in situations where other treatments are ineffective or not tolerated. This assessment is to be made before sodium valproate is prescribed for the first time, or when a woman of child-bearing potential treated with sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Women of child-bearing potential should be informed of the risks and benefits of the use of valproate during pregnancy.

Treatment advice:

It is recommended that women of child-bearing potential taking sodium valproate should:

• receive counselling with regard to the risk of foetal abnormalities;

• have their drug treatment reviewed before conception. This may involve dose adjustments or alternative therapy options. If sodium valproate is to be continued, monotherapy should be used if possible at the lowest effective dose given in divided doses, as risk of abnormality is greater in women taking combined medication and in women taking a higher total daily dose;

• undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;

• take folic acid supplementation (5mg daily) for at least 4 weeks prior to and 12 weeks after conception as folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy.

It is recommended that in bipolar disorders indication, cessation of valproate therapy should be considered.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to thrombocytopenia, hypofibrinaemia and/or to a decrease in other coagulation factors. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce haemorrhagic syndrome as they decrease the vitamin-K factors. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

2.4 Actions taken by international regulators

2.4.1 EMA

On 10 October 2013, the European Medicines Agency (EMA) started a review of valproate and related substances use in pregnancy under Article 31 of Directive 2001/83/EC. This review was initiated at the request of the UK Medicines and Healthcare Products Regulatory Agency (MHRA) following the publication of new studies suggesting that in some children problems in neurodevelopment, which can include autism, may be long-lasting. On 19 November 2014, the Coordination group for Mutual recognition and Decentralized procedure human (CMDh) adopted by consensus the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation and the EMA agreed on measures to strengthen warning and restrictions on valproate use in women and girls, due to the risk of malformations and neurodevelopmental disorders in babies who are exposed to valproate in the womb and also recommended studies (Drug Utilization Study and prescriber survey) at EU level to measure how effective the proposed risk minimization measures were.

The 2014 review also recommended studies at EU level to measure how effective the proposed measures were. Some EU member states have since carried out additional assessments of the impact of the measures at national level and concerns have been raised about how effective the measures have been in increasing awareness and reducing valproate use appropriately in its various indications. The French medicines regulator, ANSM, therefore asked EMA to review the effectiveness of the measures and to consider whether further EU-wide action should be recommended to minimise the risks in women who are pregnant or of childbearing age.

2.4.2 FDA

The United States Food and Drug Administration (FDA) issued a safety communication in May 2013 regarding the risks of valproate in pregnancy.

‘The U.S. Food and Drug Administration (FDA) is advising health care professionals and women that the anti-seizure medication valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. Based on information from a recent study, there is evidence that these medications can cause decreased IQ scores in children whose mothers took them while pregnant. Stronger warnings about use during pregnancy will be added to the drug labels, and valproate’s pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug).

With regard to valproate use in pregnant women with epilepsy or bipolar disorder, valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder.

With regard to women of childbearing age who are not pregnant, valproate should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should use effective birth control.’

3.0 SCIENTIFIC INFORMATION

3.1 Company report

Sanofi has provided their response to the PRAC list of questions (see Annex 1 for full report).

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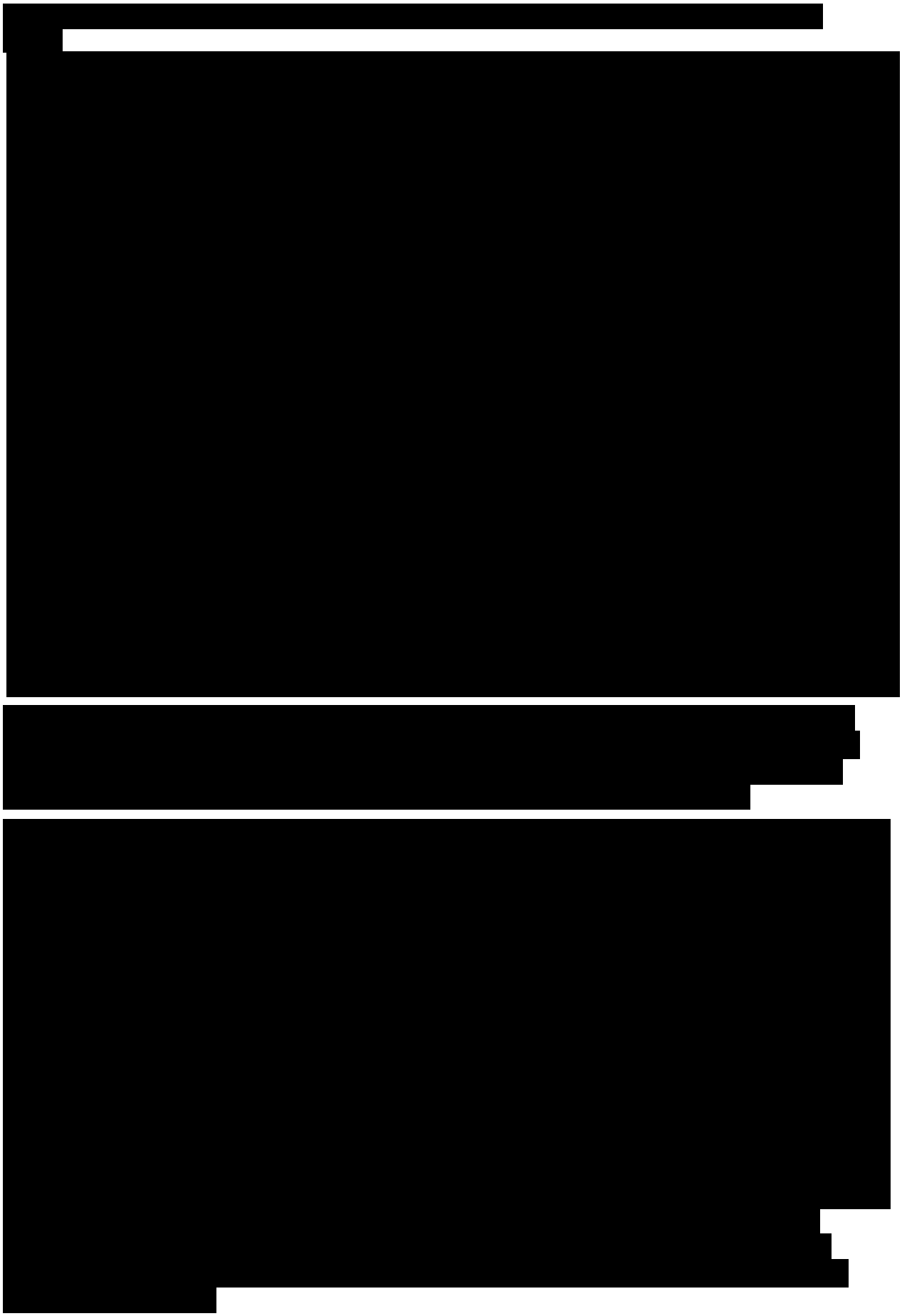

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3.1.3 Review of the literature

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3.2 Information from France

The French agency (ANSM) triggered the current EU referral which started in March 2017. Since the referral began ANSM have contraindicated the use of sodium valproate in pregnant women and women of childbearing age not using effective contraception for the bipolar indication. ANSM states that this action was taken because more women of childbearing age are treated with valproate for bipolar disorder than epilepsy. It was also noted that most women taking valproate for bipolar disorder stop therapy in the first trimester and no patient treated for bipolar disorder has been identified who only tolerates valproate.

3.2.1 Exposure to sodium valproate in pregnancy in France

An observational study was conducted with the CNAMTS (national sickness insurance fund for employees) using data from the SNIIRAM (national interregional health insurance system), the results are published on the ANSM website. The study identified pregnant women from 1 January 2007 to 31 December 2014. The indication for prescription was identified and the speciality of the prescriber.

The results showed that around 2 pregnancies per 1000 were exposed to sodium valproate between 2007 and 2014. There was a 42% decrease in exposure over this time period, but it still remains high.

A total of 14,322 pregnancies were exposed between 2007 and 2014 (Figure 2).

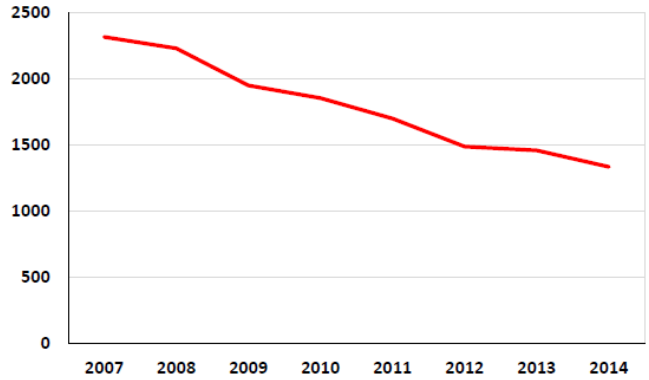


Figure 2: Number of pregnancies exposed to sodium valproate in France.

The indication for use of sodium valproate is shown in Figure 3. The number of women with epilepsy taking sodium valproate in pregnancy has reduced. However, the number of women taking sodium valproate for bipolar disorder remains static.

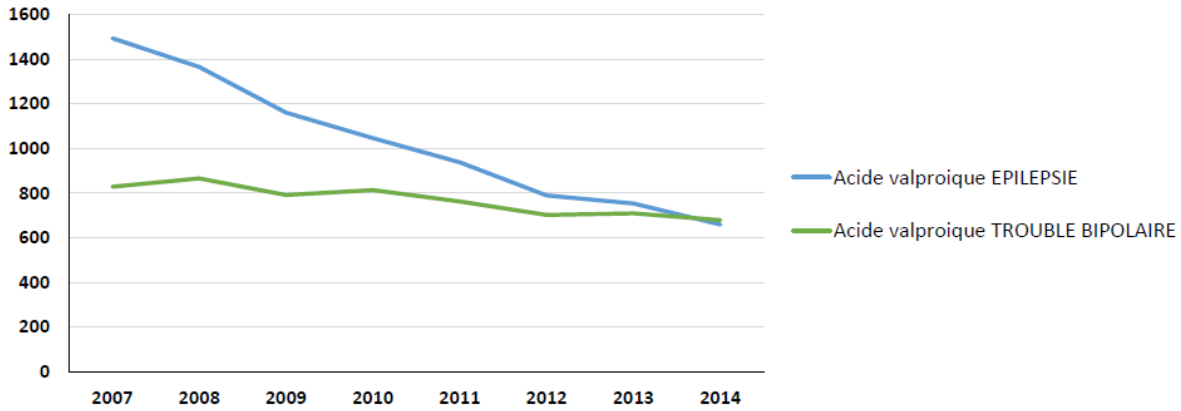


Figure 3: Number of pregnancies exposed to sodium valproate in different indications in France

Sodium valproate is one of the most widely used treatments in WCBP for bipolar disorder in France. Although this may be starting to change (Figure 4).

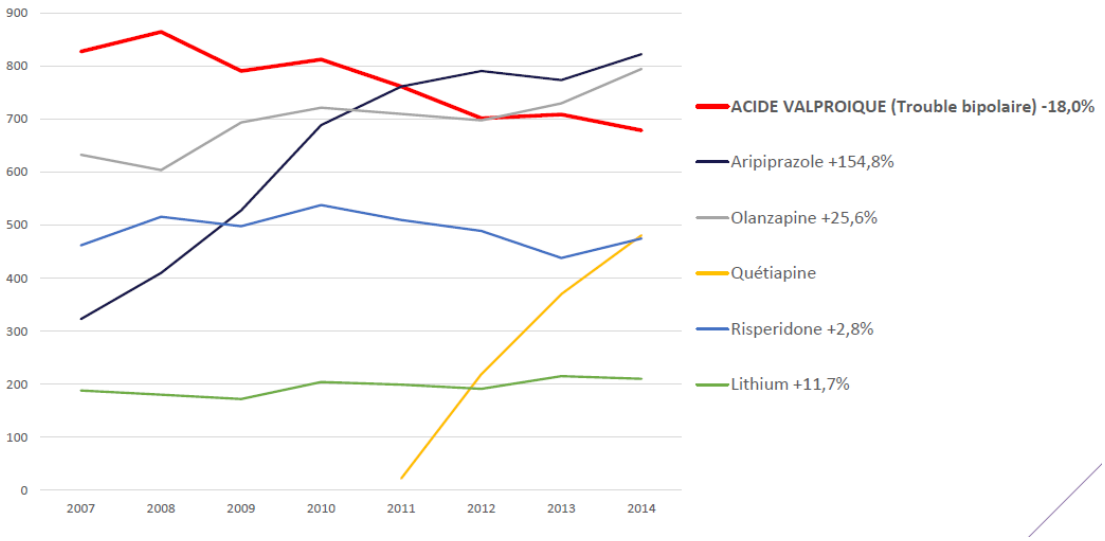


Figure 4: Number of pregnancies exposed to different medicines for bipolar disorder treatment in France

The timing of exposure during pregnancy was different between the two indications. The majority of women taking sodium valproate for bipolar disorder stopped treatment in the first trimester (Figure 5).

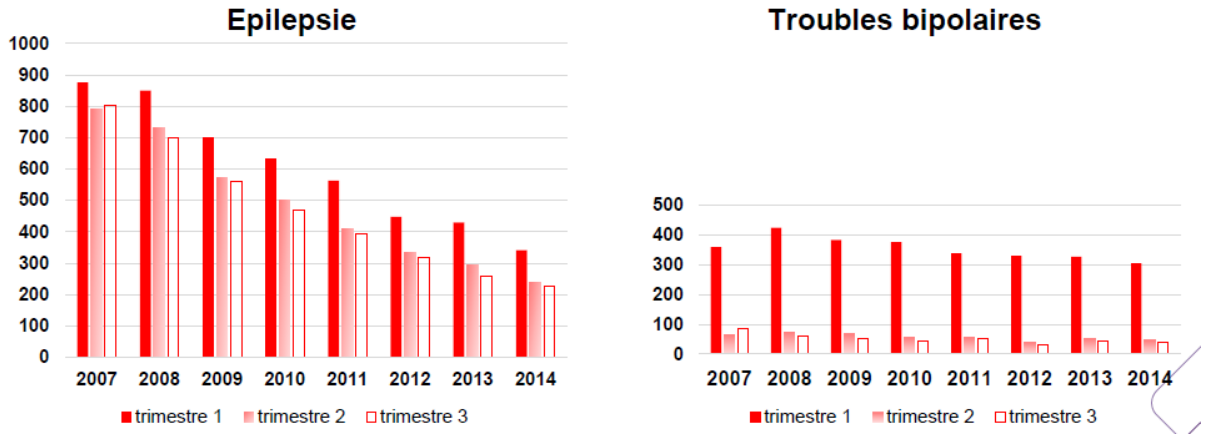


Figure 5: Timing of exposure to sodium valproate in France

The dose of sodium valproate was generally lower in women with bipolar disorder: 46% were taking < 700mg compared to 26% of women with epilepsy. The speciality of the prescriber is shown in Table 22 below.

Table 22: Prescribers of sodium valproate in pregnancy in France

Spécialité du prescripteur*	Epilepsie (n=8 204)	Troubles bipolaires (n=6 149)
Médecin hospitalier	1 595 (19,4%)	2 011 (**32,7%**)
Généraliste libéral	5 496 (**67,0%**)	2 342 (**38,1%**)
Psychiatre libéral	128 (1,6%)	1 701 (**27,7%**)
Neuropsychiatre libéral	29 (0,4%)	40 (0,7%)
Neurologue libéral	755 (9,2%)	11 (0,2%)
Autre spé. libérale	201 (2,5%)	44 (0,7%)

Of the 14,322 pregnancies there were 8,701 live births (accouchements), 115 stillbirths (autres), 4,300 terminations and 1,206 miscarriages (interruptions grossesses) (Figure 6).

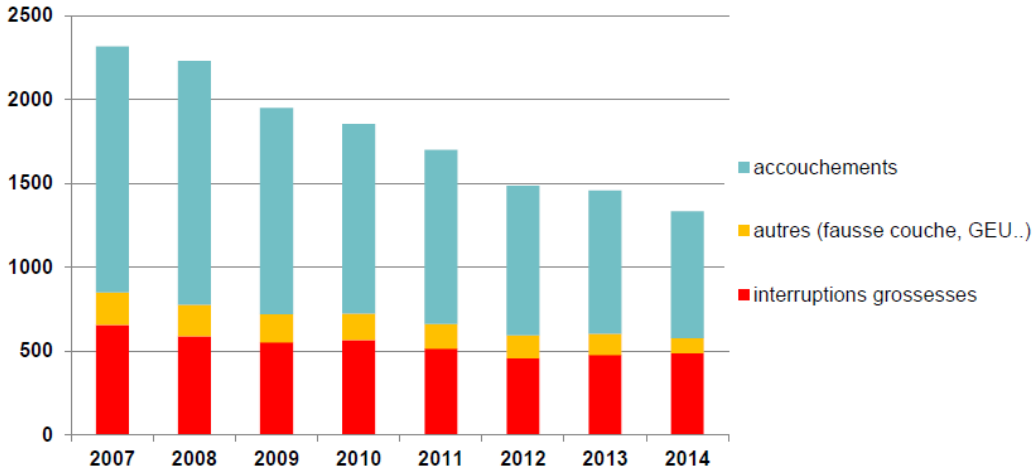


Figure 6: Outcomes of pregnancies exposed to sodium valproate in France

In a second study, data from which was published more recently, the same group looked at congenital malformations diagnosed in children exposed to sodium valproate *in utero*.

The exposure data was linked to information about the child. This linkage was partially available from 2011 (58%). Therefore, this study included data on births, stillbirths and medical terminations (from 22 weeks) from 1 January 2011 to 31 March 2015. A total of 26 major congenital malformations (MCMs) identifiable from the information in the national interregional health insurance system:

SNIIRAM were selected for study. The risk of MCM was compared between pregnancies exposed to sodium valproate monotherapy and unexposed pregnancies (no medicine for epilepsy or bipolar disorder). In addition, some comparisons were made between valproate monotherapy and lamotrigine.

In order to evaluate the total number of cases of MCM among live births exposed to valproate the group extrapolated back to 1967 when valproate was first approved. The group took into account the different marketing years for the different indications and used several hypotheses on the temporal evolution and number of pregnancies exposed and the proportion of live births. The number of live births from pregnancies exposed between 1967 and 2016 was assessed based on sales data and the study above. The number of children born alive with an MCM was calculated from the rates of MCM among live births in the general population and the risk of MCM determined from the study.

From 1 January 2011 to 31 March 2015 there were 1,897,359 pregnancies of which 1,345 were exposed to valproate.

A total of 43 cases of MCM were identified born to mothers with epilepsy taking valproate rate 46.5 per 1,000 the unexposed rate was 10.2 per 1,000. There was an increased risk of spina bifida, interventricular communication, inter-arterial communication, pulmonary artery atresia, left ventricular hypoplasia, cleft palate, anorectal atresia, hypospadias, pre-axial polydactyly. The risk increased with increasing dose.

A total of 16 cases of MCM were identified born to mothers with bipolar disorder taking valproate rate 22.2 per 1000. There was an increased risk of hypospadias, craniosynostosis.

Over the period 1967 to 2016 the group calculated that between 64,100 and 100,000 pregnancies would have been exposed to sodium valproate. This would have resulted in between 2150 and 4100 children affected by at least one MCM. It is noted that this range is based on unverifiable assumptions and should therefore be interpreted with caution.

Comments
Only a summary of the data from the second study has been published therefore it is difficult to assess the validity of the conclusions.

3.3 Published Literature

A summary of recent published literature on use of sodium valproate in pregnancy is summarised below. This is not a comprehensive review but is provided as a reminder of the nature of the safety concerns.

3.3.1 Weston et al.2016 Cochrane review on malformations [6]

This Cochrane review was performed to assess the effects of prenatal exposure to AEDs on the prevalence of congenital malformations in the child. The primary outcome was the proportion of children who presented with any type of major congenital malformation. The secondary outcomes were specific malformations: neural tube malformations, cardiac malformations, orofacial cleft/craniofacial malformation, skeletal or limb malformations and all minor congenital malformations (including minor malformations of facial features and limbs).

The authors searched the Cochrane Epilepsy Group Specialized Register (September 2015), Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 11), MEDLINE (via Ovid) (1946 to September 2015), EMBASE (1974 to September 2015), Pharmline (1978 to September 2015), Reprotox (1983 to September 2015) and conference abstracts (2010-2015) without language restriction.

The authors included prospective cohort controlled studies, cohort studies set within pregnancy registries and randomised controlled trials. Participants were women with epilepsy taking AEDs; the two control groups were women without epilepsy and women with epilepsy who were not taking AEDs during pregnancy.

Three authors independently selected studies for inclusion. Five authors completed data extraction and risk of bias assessments. Where meta-analysis was not possible, the authors reviewed included studies narratively. 50 studies were included, with 31 contributing to meta-analysis. Study quality varied, and given the observational design, all were at high risk of certain biases. However, biases were balanced across the AEDs investigated and the authors believe that the results are not explained by these biases.

Children exposed to carbamazepine were at a higher risk of malformation than children born to women without epilepsy (N = 1,367 vs 2,146, risk ratio (RR) 2.01, 95% confidence interval (CI) 1.20 to 3.36) and women with untreated epilepsy (N = 3,058 vs 1,287, RR 1.50, 95% CI 1.03 to 2.19).

Children exposed to phenobarbital (PB) were at a higher risk of malformation than children born to women without epilepsy (N = 345 vs 1,591, RR 2.84, 95% CI 1.57 to 5.13).

Children exposed to phenytoin (PHT) were at an increased risk of malformation compared with children born to women without epilepsy (N = 477 vs 987, RR 2.38, 95% CI 1.12 to 5.03) and to women with untreated epilepsy (N = 640 vs 1,256, RR 2.40, 95% CI 1.42 to 4.08).

Children exposed to topiramate (TPM) were at an increased risk of malformation compared with children born to women without epilepsy (N = 359 vs 442, RR 3.69, 95% CI 1.36 to 10.07).

The children exposed to valproate (VPA) were at a higher risk of malformation compared with children born to women without epilepsy (N = 467 vs 1,936, RR 5.69, 95% CI 3.33 to 9.73) and to women with untreated epilepsy (N = 1,923 vs 1,259, RR 3.13, 95% CI 2.16 to 4.54) (Figure 7).

There was no increased risk for major malformation for lamotrigine (LTG). Gabapentin (GBP), levetiracetam (LEV), oxcarbazepine (OXC), primidone (PRM) or zonisamide (ZNS) were not associated with an increased risk, however, there were substantially fewer data for these medications.

For AED comparisons, children exposed to VPA had the greatest risk of malformation (10.93%, 95% CI 8.91 to 13.13).

In the meta-analyses a consistent pattern emerged: children exposed to VPA were at an increased risk of both a higher overall malformation risk and risk of a specific malformations including neural tube, cardiac, oro-facial cleft and craniofacial and skeletal and limb malformations (Figure 8).

The prevalence of major malformation following exposure to VPA in the womb was 10.93%, once variation between the studies had been taken into consideration. Children exposed to VPA were at an increased risk of being born with a malformation compared with both the children of women without epilepsy and the children of women with untreated epilepsy, with the risk difference being 8% and 6% compared with the respective control groups.

Analysis of the risks associated with VPA treatment at the specific malformation level was limited by a lack of control data; however, children exposed to VPA remained at a significantly increased risk for neural tube, cardiac and skeletal malformations compared with control children.

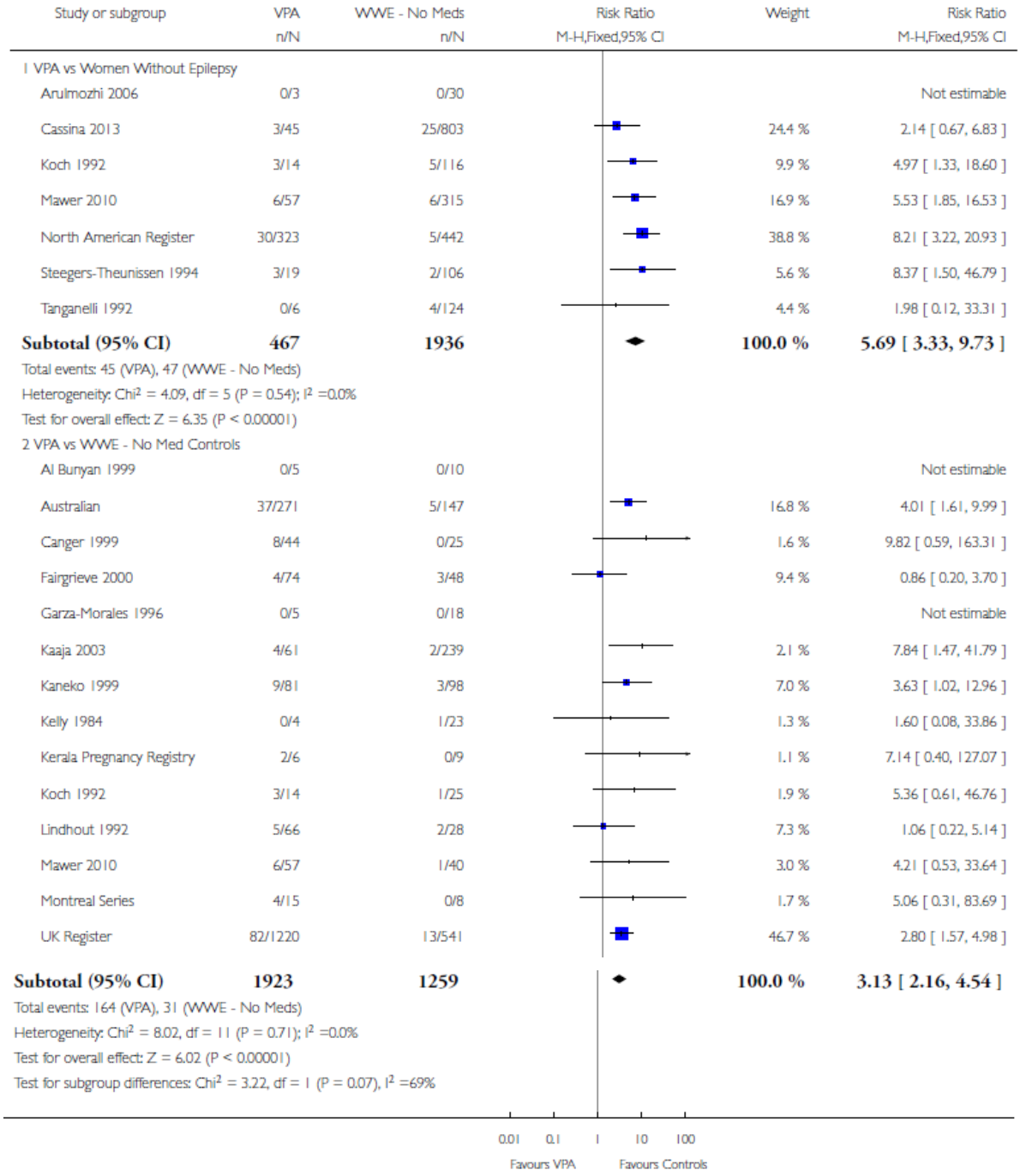


Figure 7: VPA versus controls for all major malformations

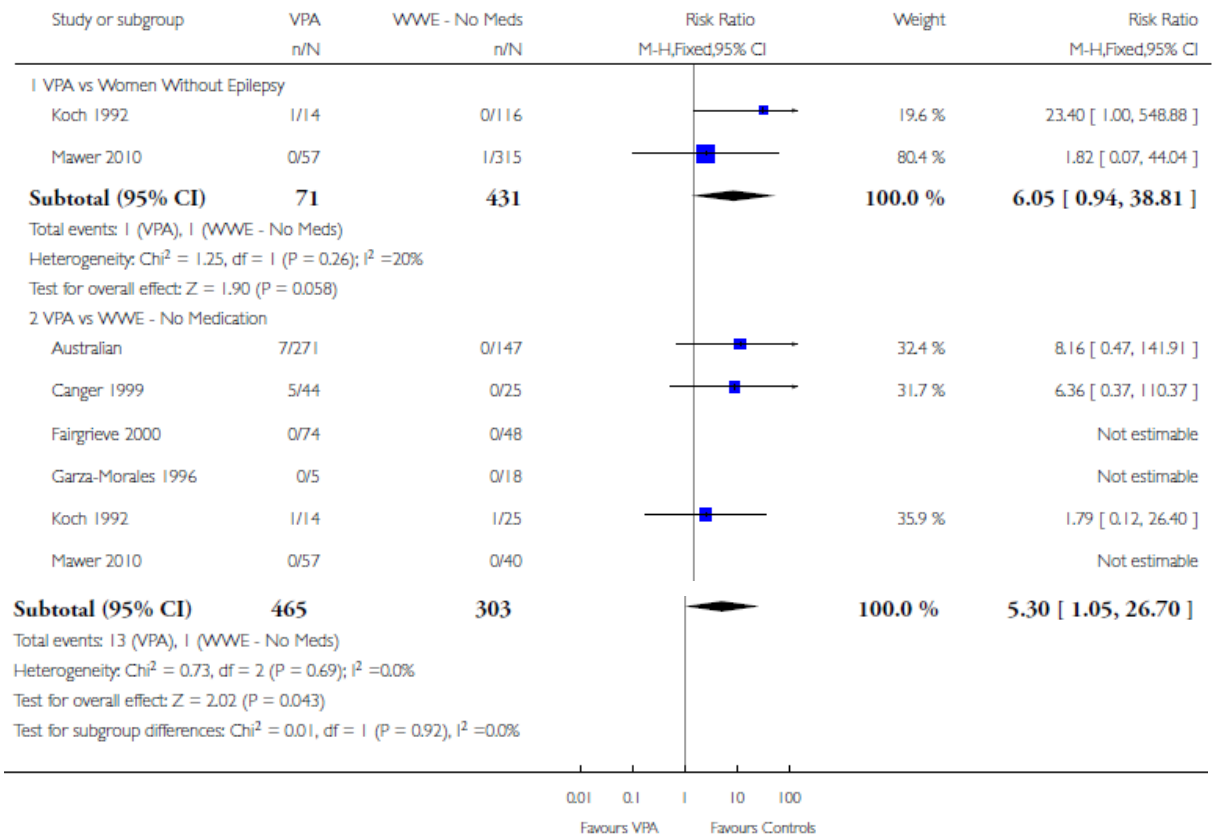


Figure 8: VPA versus controls for neural tube malformations

Children exposed to VPA were at an increased risk of malformation compared with children exposed to

- Carbamazepine (N = 2,529 vs 4,549, RR 2.44, 95% CI 2.00 to 2.94)
- Gabapentin (N = 1,814 vs 190, RR 6.21, 95% CI 1.91 to 20.23)
- Levetiracetam (N = 1,814 vs 817, RR 5.82, 95% CI 3.13 to 10.81)
- Lamotrigine (N = 2,021 vs 4,164, RR 3.56, 95% CI 2.77 to 4.58)
- Topiramate (N = 1,814 vs 473, RR 2.35, 95% CI 1.40 to 3.95)
- Oxcarbazepine (N = 676 vs 238, RR 3.71, 95% CI 1.65 to 8.33)
- Phenobarbital (N = 1,137 vs 626, RR 1.59, 95% CI 1.11 to 2.29)
- Phenytoin (N = 2,319 vs 1,137, RR 2.00, 95% CI 1.48 to 2.71)
- Zonisamide (N = 323 vs 90, RR 17.13, 95% CI 1.06 to 277.48).

At the specific malformation level, children exposed to VPA were at an increased risk of neural tube malformation compared with the children exposed to carbamazepine, levetiracetam, lamotrigine, phenobarbital and phenytoin, with the increases in risk ranging from 1% to 4%. The authors did not note any increase compared to children exposed to gabapentin, oxcarbazepine or topiramate, but this could be due to limited data (Figure 8).

The authors found significantly higher rates of specific malformations associating phenobarbital exposure with cardiac malformations and valproate exposure with neural tube, cardiac, oro-facial/craniofacial, and skeletal and limb malformations in comparison to other AEDs. Dose of exposure mediated the risk of malformation following VPA exposure; a potential dose-response association for the other AEDs remained less clear.

Exposure in the womb to certain AEDs carried an increased risk of malformation in the foetus and may be associated with specific patterns of malformation. Based on current evidence, levetiracetam and lamotrigine exposure carried the lowest risk of overall malformation; however, data pertaining

to specific malformations are lacking. Physicians should discuss both the risks and treatment efficacy with the patient prior to commencing treatment.

Comments
This analysis confirms the adverse effects of sodium valproate exposure in pregnancy. It should be noted that congenital malformation are also associated with other anti-epileptics.

3.3.2 Veroniki et al. 2017 meta-analysis of congenital malformations [14]

The authors aimed to compare the risk of congenital malformation in infants/children who were exposed to different AEDs *in utero* through a systematic review and Bayesian random-effects network meta-analysis.

MEDLINE, EMBASE, and Cochrane CENTRAL were searched from inception to 15 December 2015. Two reviewers independently screened titles/abstracts and full-text papers for experimental and observational studies comparing mono- or poly-therapy AEDs versus control (no AED exposure) or other AEDs, then abstracted data and appraised the risk of bias. The primary outcome was incidence of major congenital malformations, overall and by specific type (cardiac malformations, hypospadias, cleft lip and/or palate, club foot, inguinal hernia, and undescended testes).

A random-effects meta-analysis model was applied because the studies differed methodologically and clinically. Outcome data were pooled using the odds ratio (OR) and, for two or more studies, the OR was estimated using Bayesian hierarchical models and a Markov Chain Monte Carlo algorithm. When treatment comparisons formed a connected network of evidence, a random-effects network meta-analysis (NMA) was conducted using treatment nodes pre-specified by the team. Multiple doses were combined in nodes, because this information was not reported consistently across the studies.

In both pairwise meta-analyses and NMAs, the authors assumed common within-network between-study variance ($\tau 2$) across treatment comparisons, since there were many treatment comparisons, including a single study where the ($\tau 2$) was not estimable.

For each outcome, the entire network was evaluated for inconsistency using the design-by-treatment interaction model sensitivity analyses were conducted on the same outcomes restricting to studies with treatment indication (ie, including only women with epilepsy), timing of at least first trimester exposure, large study size (ie, > 300 patients), maternal alcohol intake, and higher methodological quality using two items of the Newcastle-Ottawa Scale for cohort studies (adequacy of follow-up of cohorts, comparability of cohorts) and low overall risk-of-bias for randomised controlled trials (component approach using randomization and allocation concealment items).

The safety of AED medications was ranked using the surface under the cumulative ranking (SUCRA) curve. The larger the SUCRA value for a treatment, the higher its safety rank among all the available treatment options. Ideally, one would like to observe a steep gradient in the SUCRA curve suggesting that the corresponding treatment is most likely the safest. A rank-heat plot was used to depict the SUCRA values for all outcomes.

After screening 5,305 titles and abstracts, 642 potentially relevant full-text articles, and 17 studies from scanning reference lists, 96 studies were eligible (n = 58,461 patients) see Figure 9.

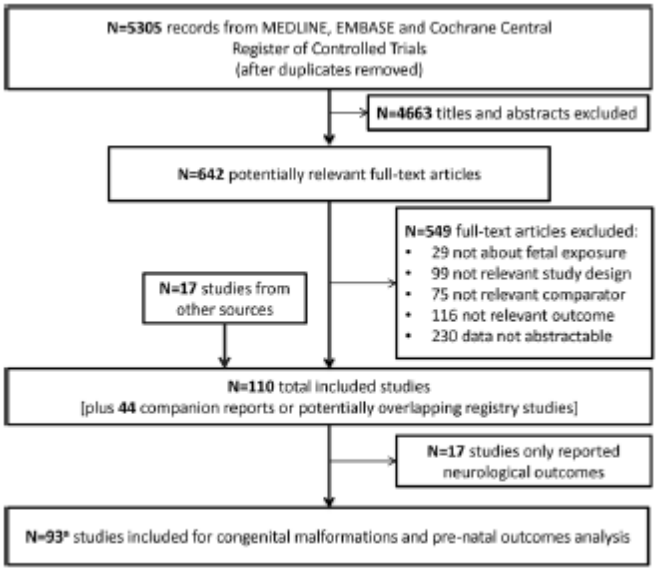


Figure 9: Study flow

Across all major congenital malformations, many AEDs were associated with higher risk compared to control (Figure 11). For major congenital malformations risks were:

- ethosuximide (OR, 3.04; 95% CrI, 1.23–7.07)
- valproate (OR, 2.93; 95% CrI, 2.36–3.69)
- topiramate (OR, 1.90; 95% CrI, 1.17–2.97)
- phenobarbital (OR, 1.83; 95% CrI, 1.35–2.47)
- phenytoin (OR, 1.67; 95% CrI, 1.30–2.17)
- carbamazepine (OR, 1.37; 95% CrI, 1.10–1.71)

In addition, 11 poly-therapies were significantly more harmful than control.

Lamotrigine (OR, 0.96; 95% CrI, 0.72–1.25) and levetiracetam (OR, 0. 72; 95% CrI, 0.43–1.16) were not associated with congenital malformations.

There is concern that most AEDs introduce the risk of abnormal or delayed physical development for infants who are exposed *in utero*. These results show that, across major and minor congenital malformations outcomes, many AEDs were associated with higher risk of congenital malformations than control (Figures 10 - 14).

The monotherapies associated with statistically significant risk of congenital malformations (CMs) and prenatal harms compared to control across two or more NMAs were:

- carbamazepine (overall major and minor CMs),
- clobazam (prenatal growth retardation, preterm birth),
- ethosuximide (overall major CM, cleft lip/palate, club foot),
- gabapentin (cardiac malformations, hypospadias),
- phenobarbital (overall major CM, prenatal growth retardation, cleft lip/palate),
- phenytoin (overall major CM, cleft lip/palate, club foot),
- topiramate (overall major CM, combined fetal losses, prenatal growth retardation, cleft lip/palate), and
- valproate (overall major and minor CMs, combined fetal losses, hypospadias, cleft lip/palate, club foot).

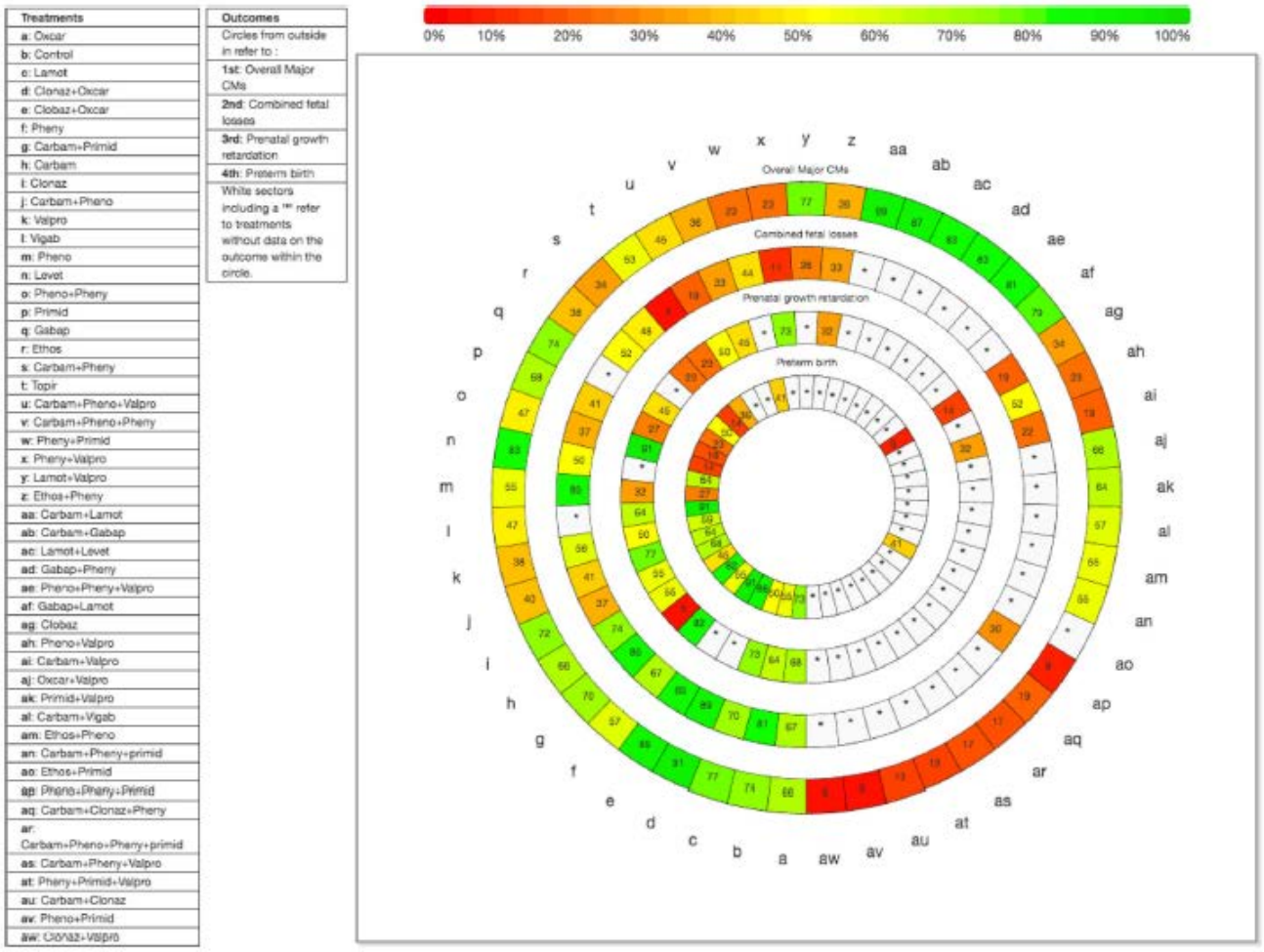


Figure 10: Rank heat plot for overall major congenital malformations (CMs), combined fetal losses, prenatal growth retardation, and preterm birth. Rank-heat plot of 49 treatments (presented in 49 radii) and four outcomes (presented in four concentric circles). Each sector is coloured according to the SUCRA value of the corresponding treatment and outcome using the transformation of three colours: red (0%), yellow (50%), and green (100%). carbam carbamazepine, clobaz clobazam, clonaz clonazepam, ethos ethosuximide, gabap gabapentin, lamot lamotrigine, levet levetiracetam, oxcar oxcarbazepine, pheno phenobarbital, pheny phenytoin, primid primidone, topir topiramate, valpro valproate, vigab vigabatrin

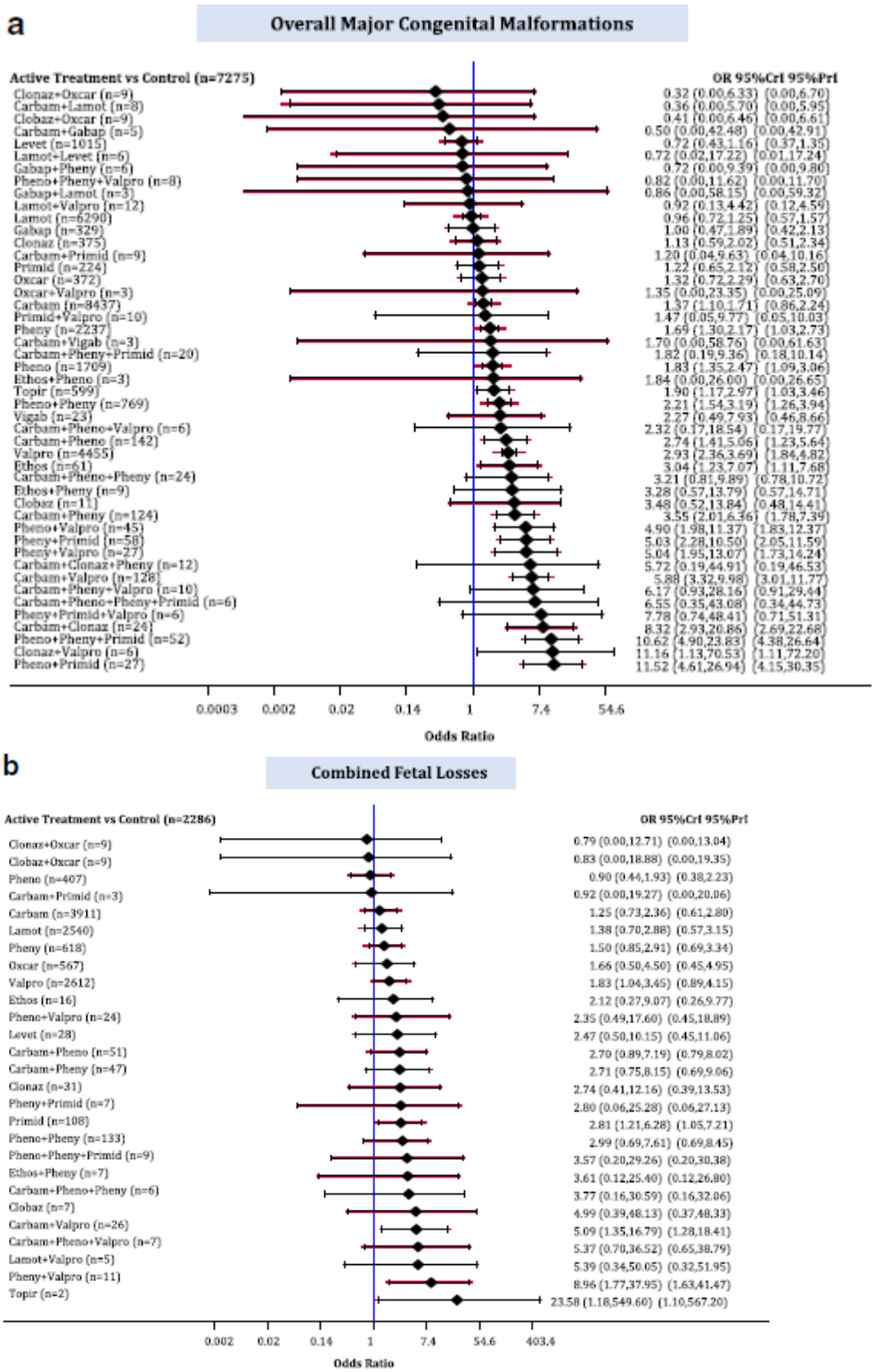


Figure 11: Network meta-analysis forest plots for each treatment versus control. Each rhombus represents the summary treatment effect estimated in the network meta-analysis on the odds ratio (OR) scale. The black horizontal lines represent the credible intervals (CrI) for the summary treatment effects, and the red horizontal lines represent the corresponding predictive intervals (PrI). In the absence of heterogeneity, the CrIs and PrIs should be identical. The vertical blue line corresponds to an OR = 1. The total sample size (n) included in each treatment is also presented**. a Overall major congenital malformations (78 studies, 35,016 cases, 48 treatments). b Combined fetal losses (31 studies, 13,487 cases, 28 treatments)**

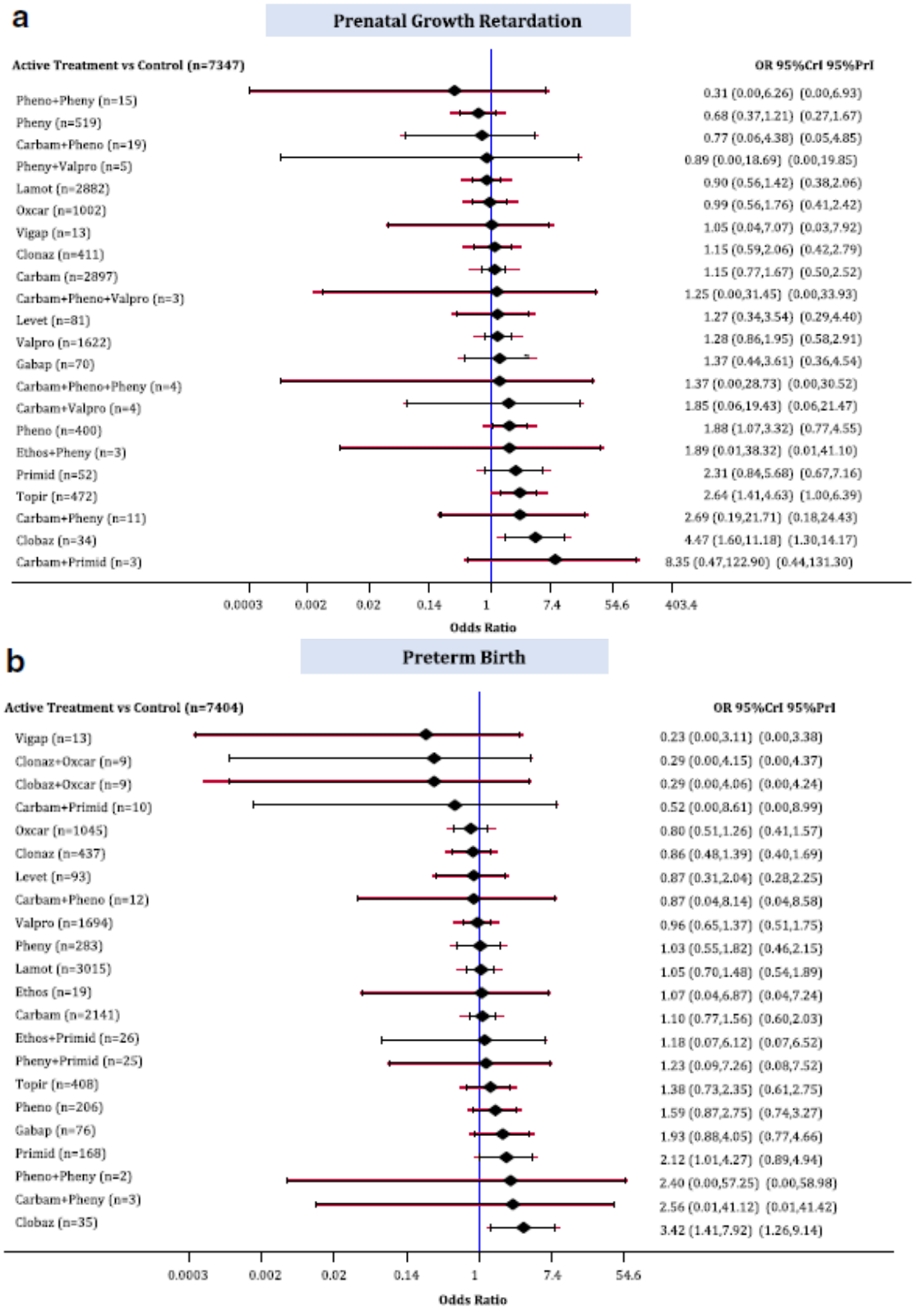


Figure 12: Network meta-analysis forest plots for each treatment versus control. Each rhombus represents the summary treatment effect estimated in the network meta-analysis on the odds ratio (OR) scale. The black horizontal lines represent the credible intervals (CrI) for the summary treatment effects, and the red horizontal lines represent the corresponding predictive intervals (PrI). The vertical blue line corresponds to an OR = 1**. a Prenatal growth retardation (16 studies, 18,177 cases, 23 treatments). b Preterm birth (17 studies, 17,133 cases, 23 treatments)**

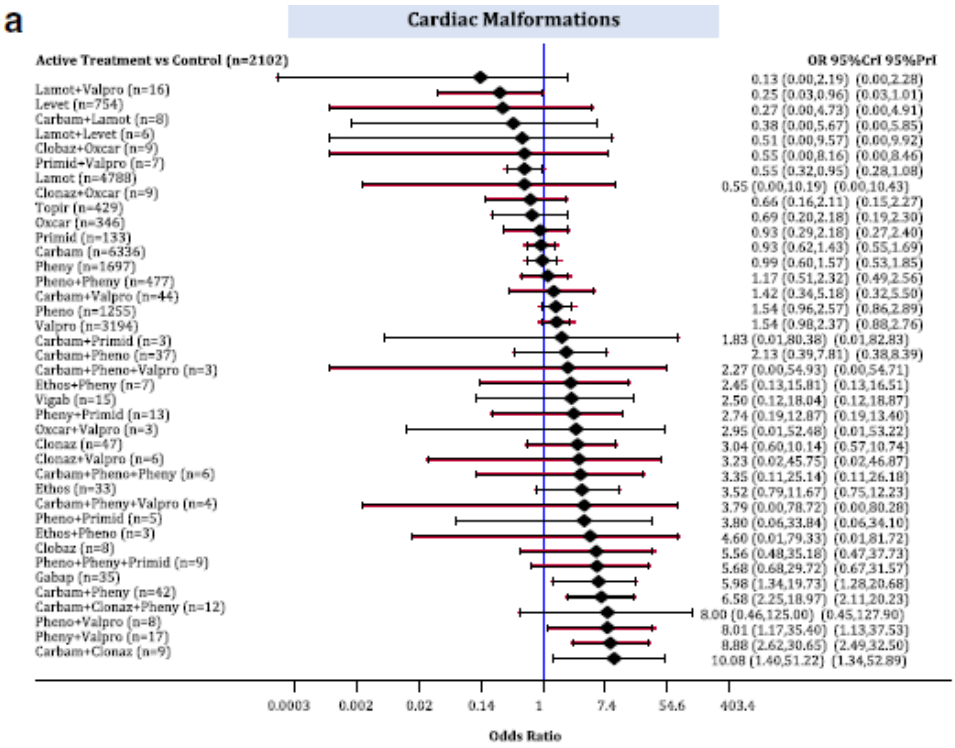


Figure 13: Network meta-analysis forest plots for each treatment versus control. Each rhombus represents the summary treatment effect estimated in the network meta-analysis on the odds ratio (OR) scale. The black horizontal lines represent the credible intervals (CrI) for the summary treatment effects, and the red horizontal lines represent the corresponding predictive intervals (PrI). In the absence of heterogeneity, the CrIs and PrIs should be identical. An OR > 1 suggests that control is safer, whereas an OR < 1 suggests that the comparator active treatment is safer. The vertical blue line corresponds to an OR = 1 (i.e., the treatment groups compared are equally safe). The total sample size (n) included in each treatment is also presented**. a Cardiac malformations (51 studies, 21,935 cases, 40 treatments).**

The study has some limitations worth noting.

First, the authors did not incorporate differences in drug dosages of the AEDs because this information was rarely reported across the included studies, although a dose-response relationship has been observed for these agents. For instance, a potential modification of the estimated treatment effects may occur if the doses vary considerably across treatment indications, and accounting for the fact that certain AEDs were more widely utilized in other conditions, while some AEDs are almost exclusively used for epilepsy.

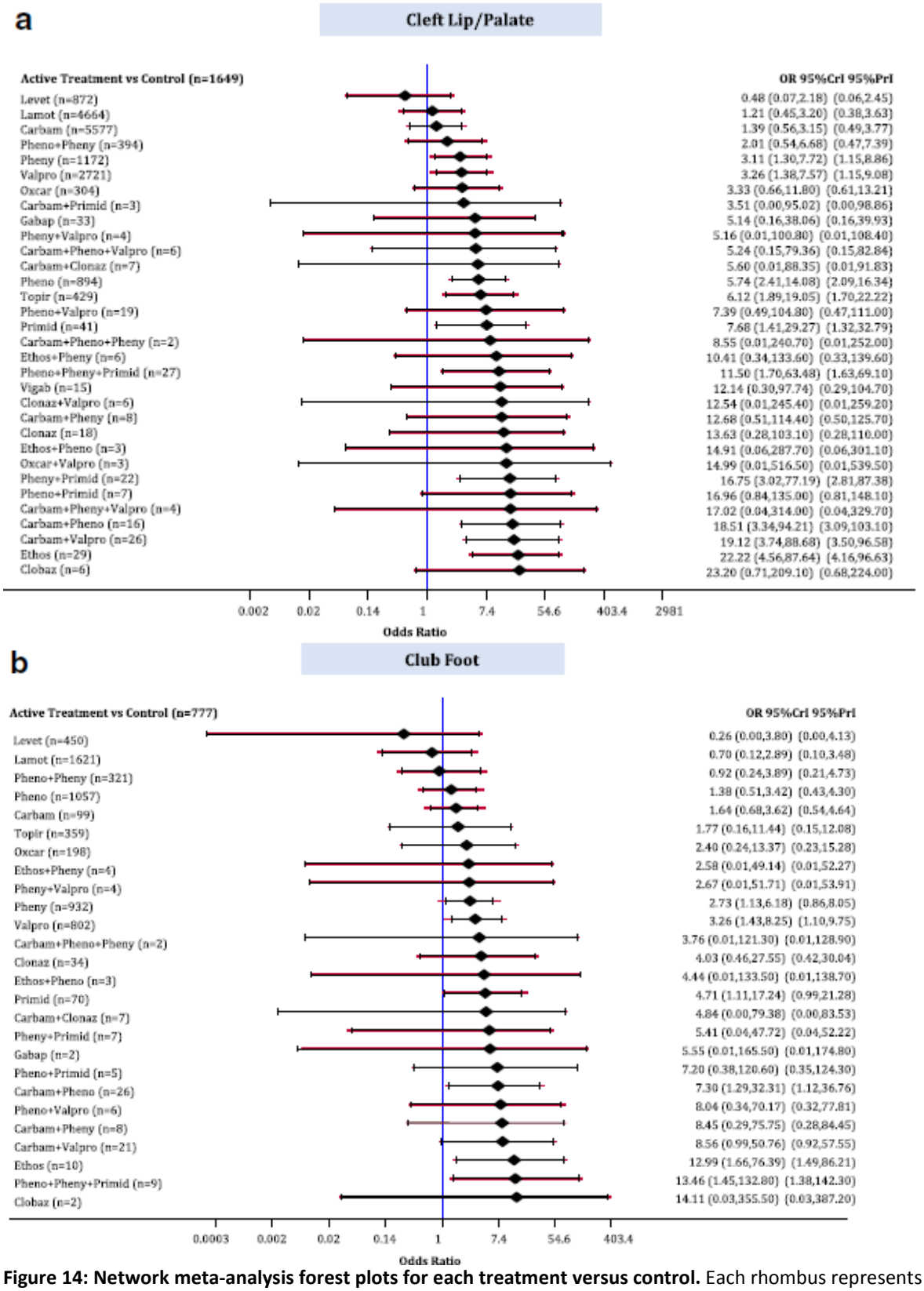


Figure 14: Network meta-analysis forest plots for each treatment versus control. Each rhombus represents the summary treatment effect estimated in the network meta-analysis on the odds ratio (OR) scale. The black horizontal lines represent the credible intervals (CrI) for the summary treatment effects, and the red horizontal lines represent the corresponding predictive intervals (PrI). The vertical blue line corresponds to an OR = 1**. a Cleft lip/palate (29 studies, 18,987 cases, 33 treatments). b Club foot (23 studies, 8836 cases 27 treatments**).

Second, the paucity of available data is a limitation; many poly-therapies were informed by only a few studies and patients, and many studies included zero events in all arms for the specific congenital malformations and were excluded from those analyses. This impacted the treatment group risk across studies; for example, the median risk of the major congenital anomalies per treatment ranged between 0% and 24%. The lack of adequate knowledge of risks for multiple AEDs impacts the NMA results. This affected the SUCRA estimates, which showed several poly-therapies with high OR estimates, but with extremely wide CrIs.

Third, quality of reporting of the identified observational studies may have introduced bias; 81% did not control for important cofounders, such as maternal age and epilepsy type and severity, and 59% had large attrition rates.

Fourth, despite no evidence of inconsistency, the assessment of transitivity for most treatment effect modifiers suggested that there was an imbalance in the different levels of quality appraisal across treatment comparisons and most outcomes, which may affect NMA results.

Fifth, although adjusted funnel plots suggested no evidence of publication bias and small-study effects, asymmetry may have been masked given several studies compared multiple arms.

Sixth, the strength of evidence in most NMAs may be low due to the small number of studies compared to the number of treatments included in each network.

Seventh, the authors combined data across study designs to determine how AEDs behave in the 'real world'. However, this may have introduced heterogeneity in the analyses.

The authors concluded that newer generation AEDs, lamotrigine and levetiracetam, were not associated with significant increased risks of congenital malformations compared to control, and were significantly less likely to be associated with children experiencing cardiac malformations than control. However, this does not mean that these agents are not harmful to infants/children exposed *in utero*. Counselling is advised concerning teratogenic risks when the prescription is written for a woman of childbearing age and before women continue with these agents when considering pregnancy, such as switching from poly-therapy to monotherapy with evidence of lower risk and avoiding AEDs, such as valproate, that are consistently associated with congenital malformations. These decisions must be balanced against the need for seizure control.

Comments
Interestingly, in this study overall risks of congenital malformations were greatest with ethosuximide when considering monotherapies. Risk was generally higher with poly-therapy particularly if this included valproate.

3.3.3 Guveli et al. 2017 focus on dysmorphic features [15]

This was a retrospective study of malformations in children born to mothers currently followed up in the authors' outpatient clinics who used or discontinued AED during their pregnancy. Their children were then investigated using echocardiography, urinary ultrasound, cranial magnetic resonance image, and examined by geneticists and paediatric dentists.

One hundred and seventeen children were included in the study (Table 23). Ninety one of these children were exposed to AED during pregnancy. The most commonly used AED were valproic acid and carbamazepine in monotherapy. The percentage of major anomaly was 6.8% in all children (Table 24).

Table 23: The features of mothers and children

Variable	On AED	Non-AED	*p* value
Mother (n=88)			
Epilepsy onset age (year)	14.7±5.8	16.1±4.1	0.34
Epilepsy type			
Idiopathic epilepsy	31	12	
Unknown epilepsy	30	5	0.08*
Symptomatic epilepsy	10	0	
Mean gestational age (year)	29.9±4.5	31.3±6.1	0.69
Seizure frequency during pregnancy			
No change	64	18	
Increased	13	6	0.39*
Decreased	14	2	
Children (n=117)			
Age (yr)	4.4±3.5	6.5±3.5	0.07
Gender (female/male)	46/45	16/10	0.32

Values are presented as mean±standard deviation, or number only.
AED, antiepileptic drug.
*Fisher exact test.

Table 24: Congenital malformations

Malformations	Drug (mg/day)	Folic acid*
Major malformations (n=8)		
Atrial septal defect+atrial septal aneurysm	VPA 300	+
Atrial septal defect	CBZ 200	+
Atrial septal defect	VPA 500+PB 150	+
Patent foramen ovale+atrial septal defect+left persistent superior vena cava	PB 300+PHT 100+CBZ 300	–
Hydronephrosis	PHT 150+OXC 1,200	–
Syndactyly	VPA 500	+
Congenital hip dislocation	VPA 1,000	+
Ventricular septal defect	*Non-AED*	+
Minor malformations (n=23)		
Left intraventricular band/t	VPA 2,000	+
Patent foramen ovale+strabismus	PB 200	+
Patent foramen ovale	CBZ 100	–
Patent foramen ovale	CBZ 200	–
Patent foramen ovale	VPA 500	+
Patent foramen ovale	OXC 900	–
Patent foramen ovale	*Non-AED*	+
Left intraventricular band/t	*Non-AED*	–
Bilateral medullar nephrocalcinosis	VPA 500	+
Bilateral medullar nephrocalcinosis	CLZ 0.5	–
Bifid renal pelvis+ptotic kidney	PB 100+PHT 100	–
Ptotic kidney	PB 300+PRM 50	–
Renal agenesis	VPA 1,000+LTG 100	–
Dilatation in pericaliceal system	VPA 500	+
Renal agenesis	*Non-AED*	–
Hyperintense noduler lesion	CLZ 50	–
Choroid fissure cyst	PB 100	–
Arachnoid cysts	VPA 500	–
Ventricular asymmetry+deep white matter lesion	PB 100	–
Periventricular leukomalacia+arachnoid cyst+cerebellar atrophy	VPA 200	–
Inguinal hernia	*Non-AED*	+
Strabismus (n=2)	VPA 2000	+

AED, antiepileptic drug; VPA, valproic acid; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; OXC, oxcarbazepine; LTG, lamotrigine; CLZ, clonazepam; PRM, primidone.
*$p>0.05$ major malformations and folic acid using.

Dysmorphic features and dental anomalies were observed more in children exposed especially to valproic acid (Table 25). Dysmorphism was detected in 79.7% of the children by the medical geneticist according to the list comprised for this study. The mean number of dysmorphic features was 3.2±7.7 in the AED group, and 0.9±2.5 in the non-AED group ($p<0.001$). Dysmorphic features had no statistically significant correlation with either mono/poly-therapy or type of epilepsy ($p>0.05$). The most common dysmorphic features were observed in children whose mothers used VPA, regardless of the daily dosage ($p<0.05$).

Table 25: Dysmorphic features and developmental dental anomalies

Dysmorphic features*	Monotherapy (n=76)						Polytherapy (n=15)	Non-AED (n=26)
	VPA	CBZ	PB	PHT	OXC	CLZ		
Eye[a]	48	25	9	1	8	2	14	8
Nose[b]	35	8	4	0	1	0	14	5
Ear[c]	3	0	1	1	0	0	1	0
Mouth[d]	23	20	7	1	2	2	13	10
Joint[e]	8	3	4	0	1	0	6	0
Others[f]	14	8	2	0	2	0	6	1
Dental anomalies[g]	11	9	6	1	2	2	9	4
Total mean number of dysmorphic features†	3.1±8.1						3.6±5.6	0.9±2.5
Total mean number of dysmorphic features for AED group	3.2±7.7							
Ratio of of dental anomalies (%)‡	53.8							23.5

Values are presented as number only, mean±standard deviation, or percent only.
AED, antiepileptic drug; VPA, valproic acid; CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; OXC, oxcarbazepine; CLZ, clonazepam.
[a]Medial deficiency of eyebrow, epicanthus, infraorbital grooves, hypertelorism, upward slanting palpebral fissures, downward slanting palpebral fissures, prominent eyelashes, telecanthus, blue sclera, supraorbital fullness; [b]Broad nasal root, short nose, anteverted nares, broad nasal tip, hypoplastic nasal alae, tubular nose; [c]Retroverted ears, low set ear; [d]Smooth philtrum, thin upper lip, thick lower lip, down turned corners of the mouth, large mouth, small mouth, high arched palate, prominent columella; [e]Hyperextensible joints, cubitus valgus, fetal finger pad, tapering fingers; [f]Broad forehead, high forehead, facial hirsuitism, nail hypoplasia, frontal bossing, micrognathia, mongolian spot, pectus excavatum; [g]Hypoplasia, delayed eruption, malocclusion, disturbances of shape, supernumerary teeth, hypodontia.
*Every patient has more than one dysmorphic feature.
†$p<0.001$ in AED and non-AED groups, but $p>0.05$ in monoteraphy and polyteraphy; ‡$p<0.05$ in AED and non-AED groups.

There were 26 mothers with two and four mothers with three pregnancies from the same fathers (Table 26).

Table 26: The conditions of children from the same parents with two or more pregnancies

Patient	1. Pregnancy AED (mg/day)	Malformation	2. Pregnancy AED (mg/day)	Malformation	3. Pregnancy AED (mg/day)	Malformation
1	CBZ 100	-	CBZ 100	PFO		
2	CBZ 800	Teeth	CBZ 800	Teeth		
3	CBZ 200+VPA 500	-	CBZ 200	PFO		
4	CBZ 300	-	CBZ 600	-		
5	VPA 500	Dilatation in pericalyxial system	VPA 500	-		
6	VPA 2,000	Strabismus	VPA 2,000	Strabismus		
7	VPA 1,000	-	VPA 1,000	-		
8	VPA 600	-	VPA 200	-		
9	VPA 1,500	Teeth	VPA 1,000	-		
10	VPA 500	Teeth	VPA 500	-	VPA 500	-
11	PB 200	Teeth	VPA 500	-		
12	PB 100	Teeth	PB 300	Teeth		
13	PHT 300	Teeth	PHT 150+PB 150	Hydronephrosis		
14	OXC 1,000	PFO	OXC 1,000	-		
15	CLZ 0.5	Teeth	CLZ 0.5	Teeth		
16	PB 25	-	Non-AED	PFO		
17	CBZ 300+PB 300+PHT 300	Teeth	CBZ 300+PB 300 +PHT 100	Teeth+PFO+ASD+ left persistant superior vena cava*	CBZ 200+PB 300 +PHT 100	Teeth
18	Non-AED	Renal agenesis	VPA 1,000	Renal agenesis		
19	Non-AED	-	Non-AED	VSD	Non-AED	-
20	Non-AED	-	Non-AED	Left intraventricular band/t		
21	Non-AED	-	VPA 500	Syndactyly		
22-25	Non-AED	-	Non-AED	-		
26	Non-AED	-	Non-AED	-	Non-AED	-

AED, antiepileptic drug; CBZ, carbamazepine; VPA, valproic acid; PB, phenobarbital; PHT, phenytoin; OXC, oxcarbazepine; CLZ, clonazepam; PFO, patent foramen ovale; ASD, atrial septal defect; VSD, ventricular septal defect.

No correlation was found between the distribution of malformations in recurring pregnancies and AED usage. For instance, in one family both siblings had renal agenesis although their mother was on AED (1,000 mg/day VPA and 100 mg/day lamotrigine [LTG]) during her first pregnancy but discontinued AEDs during her second. In another example of three siblings, their mother never used AED during pregnancies, the first and last children were healthy, whereas the second child had a major malformation. In the case of two other siblings, the first child was healthy despite being exposed to phenobarbital (25 mg/day) during pregnancy; the second child had a minor malformation, although not exposed to an AED during pregnancy.

Comments

This study was included as it provided information on the frequency of dysmorphic features in children exposed *in utero* to anti-epileptics and information on recurrence of malformation in subsequent pregnancies.

3.3.4 Bromley et al. Cochrane review of neurodevelopmental outcomes [7]

To assess the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes in the child and to assess the methodological quality of the evidence.

The authors searched the Cochrane Epilepsy Group Specialized Register (May 2014), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2014, Issue 4), MEDLINE (via Ovid) (1946 to May 2014), EMBASE (May 2014), Pharmline (May 2014) and Reprotox (May 2014). No language restrictions were imposed. Conference abstracts from the last five years were reviewed along with reference lists from the included studies.

Prospective cohort controlled studies, cohort studies set within pregnancy registers and randomised controlled trials were selected for inclusion. Participants were women with epilepsy taking AED treatment; the two control groups were women without epilepsy and women with epilepsy who were not taking AEDs during pregnancy.

The developmental quotient (DQ) was lower in children exposed to carbamazepine (n = 50) than in children born to women without epilepsy (n = 79); mean difference (MD) of -5.58 (95% CI -10.83 to -0.34, P = 0.04). The developmental quotient of children exposed to carbamazepine (n = 163) was also lower compared to children of women with untreated epilepsy (n = 58) (MD -7.22, 95% CI - 12.76 to -1.67, P = 0.01). Further analysis using a random-effects model indicated that these results were due to variability within the studies and that there was no significant association with carbamazepine.

The intelligence quotient (IQ) of older children exposed to carbamazepine (n = 150) was not lower than that of children born to women without epilepsy (n = 552) (MD -0.03, 95% CI -3.08 to 3.01, P = 0.98). Similarly, children exposed to carbamazepine (n = 163) were not poorer in terms of IQ in comparison to the children of women with untreated epilepsy (n = 87) (MD 1.84, 95% CI -2.13 to 5.80, P = 0.36).

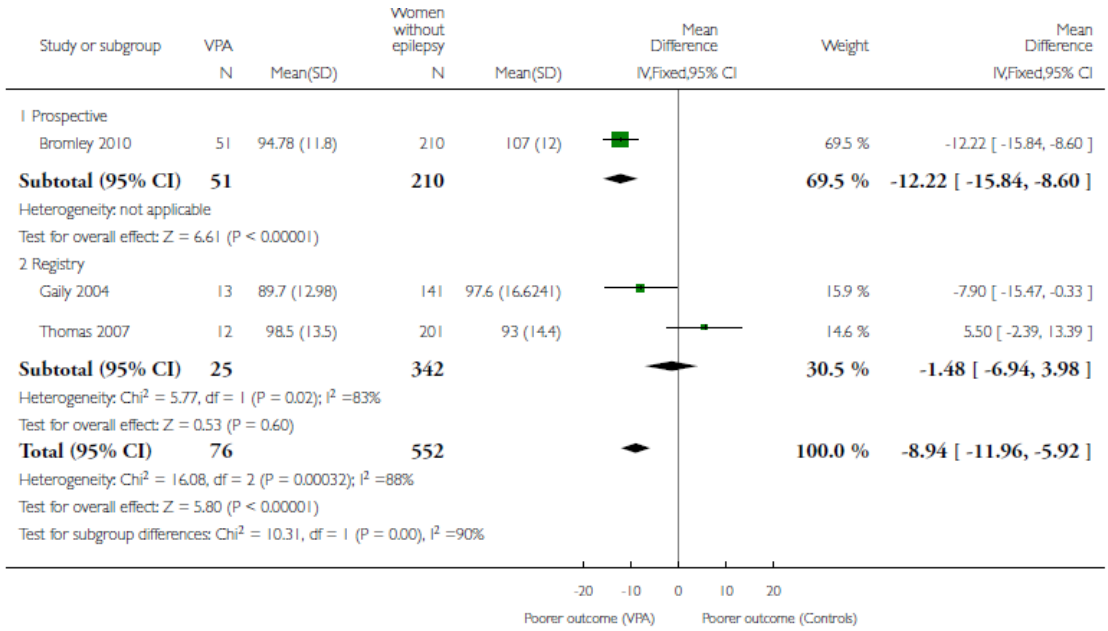


Figure 15: Comparison of valproate versus women without epilepsy for IQ

The intelligence quotient of children exposed to valproate (n = 76) was lower than for children born to women without epilepsy (n = 552) (MD -8.94, 95% CI -11.96 to -5.92, P < 0.00001) (Figure 15).

Children exposed to valproate (n = 89) also had lower intelligence quotient than children born to women with untreated epilepsy (n = 87) (MD -8.17, 95% CI -12.80 to -3.55, P = 0.0005) (Figure 16).

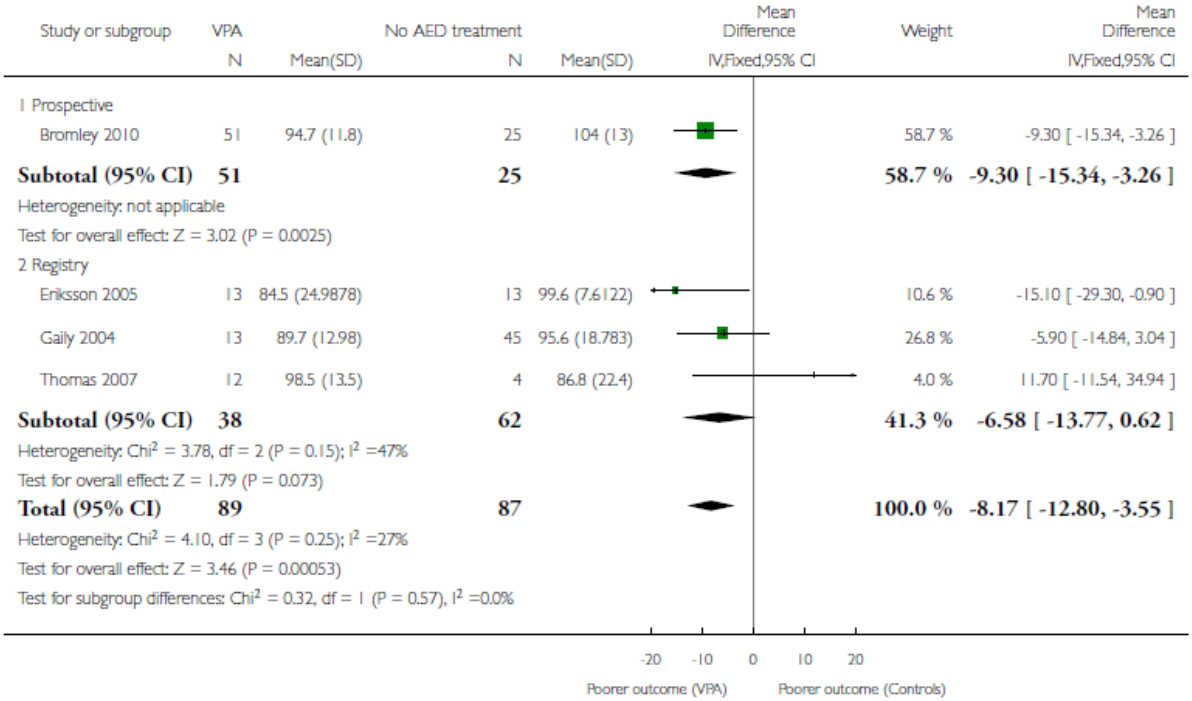


Figure 16: IQ in children exposed to valproate versus controls (women with epilepsy no AED treatment)

The DQ in children exposed to VPA (n = 123) was lower than the DQ in children of women with untreated epilepsy (n = 58) (MD -8.72, 95% -14.31 to -3.14, P = 0.002) (Figure 17).

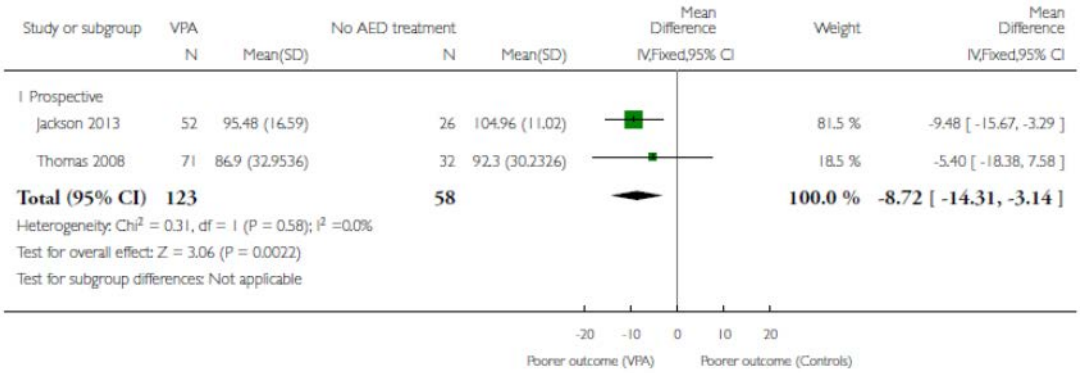


Figure 17: Development in children exposed to valproate versus controls (women with epilepsy but no treatment)

In terms of drug comparisons, in younger children there was no significant difference in the DQ of children exposed to carbamazepine (n = 210) versus valproate (n=160) (MD 4.16, 95% CI -0.21 to 8.54, P = 0.06). However, the IQ of children exposed to valproate (n = 112) was significantly lower than for those exposed to carbamazepine (n = 191) (MD 8.69, 95% CI 5.51 to 11.87, P < 0.00001).

The IQ of children exposed to carbamazepine (n = 78) versus lamotrigine (n = 84) was not significantly different (MD -1.62, 95% CI -5.44 to 2.21, P = 0.41).

There was no significant difference in the DQ of children exposed to carbamazepine (n = 172) versus phenytoin (n = 87) (MD 3.02, 95% CI -2.41 to 8.46, P = 0.28). The IQ abilities of children exposed to carbamazepine (n = 75) were not different from the abilities of children exposed to phenytoin (n = 45) (MD -3.30, 95% CI -7.91 to 1.30, P = 0.16).

IQ was significantly lower for children exposed to valproate (n = 74) versus lamotrigine (n = 84) (MD -10.80, 95% CI -14.42 to -7.17, P < 0.00001). Developmental quotient was higher in children exposed to phenytoin (n = 80) versus valproate (n = 108) (MD 7.04, 95% CI 0.44 to 13.65, P = 0.04). Similarly IQ was higher in children exposed to phenytoin (n = 45) versus valproate (n = 61) (MD 9.25, 95% CI 4.78 to 13.72, P < 0.0001).

A dose effect for valproate was reported in six studies, with higher doses (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child.

No convincing evidence of a dose effect for carbamazepine, phenytoin or lamotrigine was identified. Studies not included in the meta-analysis were reported narratively, the majority of which supported the findings of the meta-analyses.

The authors concluded that the most important finding is the reduction in IQ in the valproate exposed group, which are sufficient to affect education and occupational outcomes in later life. However, for some women valproate is the most effective drug at controlling seizures. Informed treatment decisions require detailed counselling about these risks at treatment initiation and at pre-conceptual counselling. We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.

Comments
The data only consistently shows an effect for sodium valproate. It should be noted that fewer studies were identified for inclusion in this analysis compared to the analysis on congenital malformations.

3.3.5 Baker et al. 2016 effect on intelligence quotient [16]

The authors investigated the effect of antiepileptic medicines on intelligence quotient.

Women with epilepsy (WWE) were recruited from antenatal clinics at 11 National Health Service hospitals between 2000 and 2004. The inclusion criterion was a diagnosis of epilepsy. WWE were excluded from recruitment if they had a severe learning disability or other chronic health condition requiring medication.

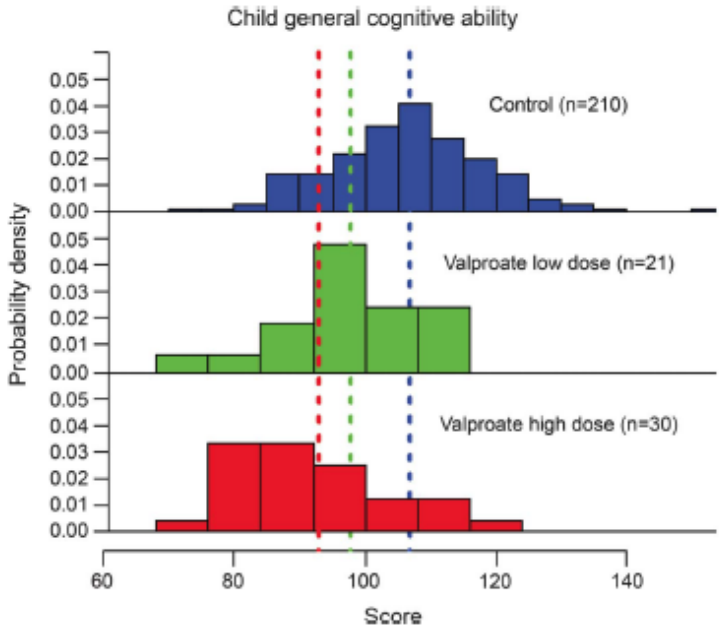
Because of the neuropsychological measures, families were required to have English as their primary language. Women without epilepsy were recruited from the same antenatal clinics. For each participant with epilepsy, a control of similar age (5/2 5 years), parity, and employment and residing within the same postal area was recruited to ensure comparable groups. The same exclusion criteria applied to the women without epilepsy. Children born to women with epilepsy (n = 5,243) and women without epilepsy (n = 5,287) were recruited during pregnancy and followed prospectively (characteristics are outlines in Table 27). Of these, 408 were blindly assessed at 6 years of age.

Table 27 Demographics and mean child IQ scores by treatment group

	Mean child IQ (SD)				Completeness of sampling			Demographics*									
								Maternal epilepsy			Seizure exposure			Maternal		Child		
	Full scale	Verbal	Nonverbal	Spatial	Initial,[b] n	Missing, n	Sampled,[a] n (%)	IGE, %	FE, %	UC, %	<20 wk, % yes	>20 wk, % yes	Convulsive,[c] %	Age, y, mean (SD)	IQ, mean (SD)	Age at assessment, mo (SD)	Gestational age, mo (SD)	Sex, % female
Controls	107 (12)	103 (12)	106 (13)	108 (13)	287	77	210 (73)	—	—	—	—	—	—	29.4 (5)	103.4 (12)	73.9 (5)	39.5 (2)	48.1
Epilepsy																		
No medication	104 (13)	99 (12)	104 (14)	105 (13)	34	9	25 (74)	32.0	40.0	28.0	16.0	8.0	4.0	25.9 (5)	96.2 (11)	75.1 (5)	39.9 (1)	28.0
Treatment																		
VPA low, ≤800 mg	98 (11)	94 (14)	98 (9)	101 (14)	25	4	21 (84)	76.2	9.5	14.3	23.8	23.8	28.6	26.4 (5)	93.8 (14)	73.0 (2)	39.6 (2)	28.6
VPA high, >800 mg	93 (12)	90 (10)	96 (15)	96 (16)	34	4	30 (88)	60.0	30.0	10.0	63.3	56.7	50.0	27.1 (7)	97.0 (11)	74.1 (4)	38.5 (2)	33.3
CBZ	105 (15)	98 (15)	108 (14)	106 (16)	59	9	50 (85)	9.8	80.4	9.8	31.4	25.5	19.6	29.4 (5)	99.4 (15)	74.1 (4)	39.3 (2)	51.0
LTG	103 (11)	99 (13)	103 (12)	107 (12)	36	7	29 (81)	23.3	56.7	20.0	40.0	40.0	40.0	27.7 (6)	100.0 (12)	73.7 (4)	39.9 (2)	56.7
Other monotherapy	98 (15)	96 (15)	101 (15)	99 (15)	14	1	13 (93)	28.6	71.4	0.0	42.9	50.0	35.7	29.9 (7)	96.8 (9)	74.0 (3)	40.1 (1)	42.9
Polytherapy																		
With VPA	98 (13)	93 (10)	100 (15)	102 (12)	30	11	19 (63)	35.0	55.0	10.0	52.4	42.9	47.6	25.7 (5)	91.6 (11)	75.4 (6)	38.9 (2)	47.6
Without VPA	103 (13)	99 (12)	105 (16)	103 (17)	11	0	11 (100)	0.0	81.8	18.2	81.8	90.9	81.8	28.8 (6)	94.7 (14)	73.7 (2)	38.8 (2)	45.5

Abbreviations: CBZ = carbamazepine; FE = focal epilepsy; IGE = idiopathic generalized epilepsy; LTG = lamotrigine; UC = unclassified; VPA = valproic acid.
[a] A number of subjects had missing covariates: maternal IQ (24), gestational age (5), socioeconomic status (1), maternal age (1), alcohol (during pregnancy) (2), and smoking (during pregnancy) (2). Three subjects had multiple missing covariates and so are counted as "missing" only once, resulting in a total of 31 subjects with at least one missing covariate.
[b] Figures inclusive of children recruited between 2000 and August 2004 who attended at least one appointment with investigators. Thirty-two children recruited were not aged 6 at study close and are therefore not reported here. An additional 7 cases excluded because of genetic or maternal conditions likely influential on cognitive development (including chromosomal disorders and hydrocephalus).
[c] Percentage of those having seizures that were convulsive, IGE, FE, or UC epilepsy type. The other monotherapy group comprised 8 cases of phenytoin, 1 vigabatrin, 1 oxcarbazepine, 2 gabapentin, and 2 topiramate.

The adjusted mean IQ was 9.7 points lower (95% CI 24.9 to 214.6; p, 0.001) for children exposed to high-dose (>800 mg daily) valproate, with a similar significant effect observed for the verbal, nonverbal, and spatial subscales (Figure 18). Children exposed to high-dose valproate had an 8-fold increased need of educational intervention relative to control children (adjusted relative risk, 95% CI 8.0, 2.5–19.7; p, 0.001). Valproate at doses <800 mg daily was not associated with reduced IQ, but was associated with impaired verbal abilities (25.6, 95% CI 211.1 to 20.1; p 5 0.04) and a 6-fold increase in educational intervention (95% CI 1.4–18.0; p 5 0.01). *In utero* exposure to carbamazepine or lamotrigine did not have a significant effect on IQ, but carbamazepine was associated with reduced verbal abilities (24.2, 95% CI 20.6 to 27.8; p 5 0.02) and increased frequency of IQ <85.



Because of the small sample size, the histograms in the figure may not look normally distributed, but the medians of the groups were very similar to the highlighted means.

Figure 18: Distribution of IQ scores across the control and valproate-exposed groups

Table 28: Child IQ scores after exposure to carbamazepine, lamotrigine and other monotherapies relative to children exposed to sodium valproate

	Full-scale IQ				Verbal				Nonverbal				Spatial			
Treatment group	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p
CBZ	4.9 (3.3) [−1.5, 11.3]	0.14	9.7 (2.9) [4.0, 15.3]	<0.001	1.4 (3.1) [−4.7, 7.6]	0.65	5.2 (2.8) [−0.4, 10.8]	0.07	8.3 (3.6) [1.2, 15.4]	0.02	10.5 (3.3) [4.1, 16.9]	0.001	3.9 (3.8) [−3.4, 11.3]	0.30	9.5 (3.4) [2.8, 16.2]	0.006
LTG	2.0 (3.6) [−5.0, 9.0]	0.58	6.8 (3.3) [0.4, 13.2]	0.04	2.8 (3.5) [−4.0, 9.6]	0.42	6.6 (3.2) [0.3, 12.9]	0.04	2.7 (4.0) [−5.1, 10.6]	0.49	5.0 (3.7) [−2.3, 12.2]	0.18	3.5 (4.2) [−4.7, 11.7]	0.40	9.0 (3.9) [1.4, 16.6]	0.02
Other monotherapy	−1.7 (4.4) [−10.2, 6.9]	0.70	3.1 (4.1) [−4.9, 11.1]	0.44	0.6 (4.3) [−7.9, 9.0]	0.90	4.4 (4.1) [−3.6, 12.4]	0.29	2.2 (4.9) [−7.4, 11.9]	0.65	4.4 (4.7) [−4.7, 13.6]	0.34	−3.4 (5.2) [−13.5, 6.7]	0.51	2.2 (4.9) [−7.4, 11.8]	0.66

Abbreviations: CBZ = carbamazepine; LTG = lamotrigine; VPA = valproic acid.
Data are coefficient (standard error) [95% confidence interval]. Statistical comparisons based on the fitted model described in table 2. No adjustments have been made for multiple comparisons.

Exposure to seizures *in utero* has been reported to be associated with reduced cognitive ability, but this has not been replicated by others and is not supported by the data here. The numbers of children exposed to frequent convulsive seizures limited the investigation here into the reported association between five or more convulsive seizures and child intelligence quotient. It is of note that the majority of prospective studies to date have failed to find a significant association between exposure to transient seizures and poorer child intelligence quotient. However, none of these studies undertook rigorous collection of seizure data. The relationship between convulsive seizure exposure and increased educational needs demonstrated here was not through an association with poorer IQ levels, and future research needs to consider both biological and postnatal environmental factors. The number of children requiring additional educational assistance is outlined in Table 29.

Table 29: Prevalence of children with additional educational needs in relation to exposure to maternal drug treatment

Group	Total	Educational needs	No educational needs	Incidence rate, %	OR (95% CI)	RR (95% CI)	p
Control	213	5	208	2.3	Reference group		
Epilepsy							
No medication	25	2	23	8.0	4.1 (0.9, 19.8)	3.9 (0.9, 13.7)	0.08
Treatment group							
VPA							
Low, ≤800 mg	21	4	17	19.1	6.6 (1.5, 30.4)	5.9 (1.4, 18.0)	0.01
High, >800 mg	30	11	19	36.7	9.6 (2.6, 35.7)	8.0 (2.5, 19.7)	<0.001
CBZ	50	5	45	10.0	3.2 (0.9, 11.5)	3.0 (0.9, 9.2)	0.07
LTG	30	1	29	3.3	1.0 (0.1, 8.7)	1.0 (0.1, 7.4)	0.99
Other monotherapy	14	5	9	35.7	23.1 (5.4, 98.6)	15.2 (4.9, 29.9)	<0.001

Abbreviations: CBZ = carbamazepine; CI = confidence interval; LTG = lamotrigine; OR = odds ratio; RR = relative risk; VPA = valproic acid.
Prevalence rates, adjusted ORs, and adjusted RRs (including 95% CIs) from the logistic regression model with educational needs as the outcome (event). Two covariates were significantly associated with educational needs: gestational age (OR 0.7, 95% CI 0.6 to 0.8; $p < 0.001$) and convulsive seizures (OR 2.9, 95% CI 1.1 to 7.9; $p = 0.03$).

The authors concluded that consistent with data from younger cohorts, school-aged children exposed to valproate at maternal doses more than 800 mg daily continue to experience significantly poorer cognitive development than control children or children exposed to lamotrigine and carbamazepine.

3.3.6 Deshmukh et al. 2016 adaptive behaviour in exposed children [17]

The aim of this study was to evaluate adaptive behaviour outcomes of children prenatally exposed to lamotrigine, valproate or carbamazepine, and to determine if these outcomes were dose-dependent.

Unfortunately, most studies investigating neurodevelopmental outcomes of exposed children have relied on language testing and IQ to assess cognitive function, while adaptive behaviour outcomes have been significantly less well-studied. Although IQ tests measure general intelligence, they neither assess functional abilities nor adaptive behaviours required for independent daily living, such as socialization, communication, self-care, and motor skills.

Table 30: Baseline characteristics

	CBZ	LTG	VPA	p-value
	N=97	N=104	N=51	
	% (no.)			
Maternal Education				**0.032**
High School or Less	2.1% (2)	6.7% (7)	9.8% (5)	
Some College	21.1% (20)	17.3% (18)	23.5% (12)	
College Graduate	38.9% (37)	38.5% (40)	52.9% (27)	
Post-Graduate	37.9% (36)	37.5% (39)	13.7% (7)	
Insurance				p=0.101
Canadian	7.5% (3)	1.2% (1)	0.0% (0)	
Medicaid	2.5% (1)	1.2% (1)	6.7% (2)	
Private	90.0% (36)	97.6% (81)	93.3% (28)	
Marital Status				**p=0.040**
Married	96.0% (48)	95.7% (88)	84.2% (32)	
Unmarried	4.0% (2)	4.3% (4)	15.8% (6)	
Multivitamin Use				p=0.114
Yes	63.8% (60)	76.0% (79)	76.5% (39)	
No	36.2% (34)	24.0% (25)	23.5% (12)	
Folic Acid Use				**p=0.017**
None	31.2% (24)	13.2% (12)	25.6% (11)	
Some	68.8% (53)	86.8% (79)	74.4% (32)	
Cigarette Exposure				p=0.675
Yes	11.6% (11)	7.7% (8)	7.8% (4)	
No	35.8% (34)	44.2% (46)	45.1% (23)	
Don't remember	52.6% (50)	48.1% (50)	47.1% (24)	
Alcohol Exposure				p=0.360
Yes	24.2% (23)	23.1% (24)	33.3% (17)	
No	75.8% (72)	76.9% (80)	66.7% (34)	
Major Malformation				**p=0.025**
Yes	6.3% (5)	3.3% (3)	15.9% (7)	
No	93.7% (74)	96.7% (89)	84.1% (37)	
Epilepsy Type[a]				**p<0.001**
IGE	5.2% (3)	18.1% (15)	60.0% (21)	
NCE	41.4% (24)	32.5% (27)	25.7% (9)	
PE	53.4% (31)	49.4% (41)	14.3% (5)	
Prenatal Seizures				**p<0.001**
Yes	16.0% (15)	39.8% (41)	16.3% (8)	
No	84.0% (79)	60.2% (62)	83.7% (41)	
Mean Maternal Age at Delivery (yr)	32.3±5.4	32.1±4.4	31.3±5.0	p=0.474
Gestational Age (wks)	38.7±2.4	38.5±1.5	38.8±1.6	p=0.434
Birth Weight (kg)	3.41±0.58	3.34±0.60	3.35±0.61	p=0.701
Birth Length (cm)	50.8±3.1	50.6±3.4	51.3±2.8	p=0.433
Interview Age (yrs)	5.3±1.1	4.6±1.1	4.9±1.1	**p<0.001**
First trimester drug dose (mg/day), avg (range)	705 (100–2000)	379 (75–1500)	771 (100–1500)	**N/A**

[a] IGE = Idiopathic Generalized Epilepsy, PE = Partial Epilepsy, NCE = Nonclassifiable Epilepsy.

Deficits in these areas have significant implications for long-term behavioural outcomes. Impairments in socialization and communication, along with repetitive, stereotyped behaviours, form the basis for diagnosis of autism spectrum disorder

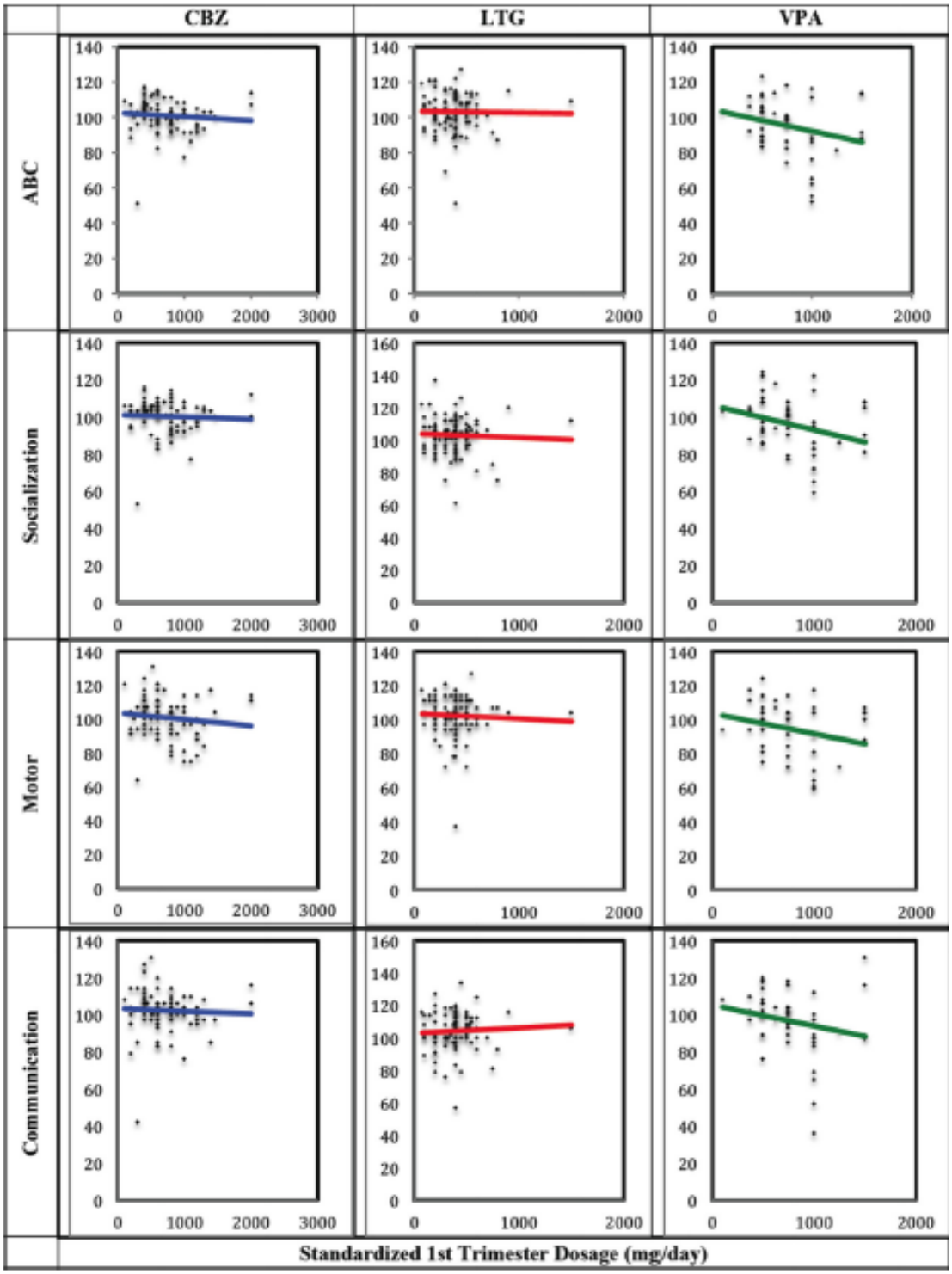


Figure 19: Scatterplots and regression lines for Adaptive Behaviour Composite (ABC), socialisation, motor and communication domain standard scores versus standardised 1st trimester dose (mg/day) for each exposure group

Data were collected from women enrolled in the North American Anti-epileptic Drug (AED) Pregnancy Registry who had taken lamotrigine, valproate or carbamazepine monotherapies throughout pregnancy to suppress seizures (Table 30).

The adaptive behaviour of 252 exposed children (including 104 lamotrigine-exposed, 97 carbamazepine-exposed, and 51 valproate-exposed), ages 3- to 6-years-old, was measured using the Vineland-II Adaptive Behaviour Scales, administered to each mother by telephone.

Mean Adaptive Behaviour Composite, domain standard scores for communication, daily living, socialization and motor skills, and adaptive levels were analysed and correlated with first trimester drug dose.

After adjusting for maternal age, education, folate use, cigarette and alcohol exposure, gestational age, and birth weight by propensity score analysis, the mean Adaptive Behaviour Composite score for valproate-exposed children was 95.6 (95% CI [91, 101]), versus 100.8 (95% CI [98, 103]) and 103.5 (95% CI [101, 106]) for carbamazepine- and lamotrigine-exposed children, respectively (ANOVA; p=0.017).

Significant differences were observed among the three drug groups in the Adaptive Behaviour Composite (p=0.017), socialization (p=0.026), and motor (p=0.018) domains, with a trend toward significance in the communication domain (p=0.053) (Figure 19, Table 31). Valproate-exposed children scored lowest and lamotrigine-exposed children scored highest in every category.

Valproate-exposed children were most likely to perform at a low or moderately low adaptive level in each category (Figure 19). Higher valproate dose was associated with significantly lower Adaptive Behaviour Composite (p=0.020), socialization (p=0.009), and motor (p=0.041) scores before adjusting for confounders. After adjusting for the above variables, increasing VPA dose was associated with decreasing Vineland scores in all domains, but the relationships were not statistically significant. No dose effect was observed for carbamazepine or lamotrigine.

Table 31: Frequency of low and moderately low adaptive levels in the overall ABC domain and subdomain categories for each group

	CBZ % (n)	LTG % (n)	VPA % (n)	P-value
ABC	5.1% (5)	2.9% (3)	19.6% (10)	**<0.001**
Communication	10.2% (10)	7.7% (8)	17.6% (9)	0.166
Receptive	11.2% (11)	3.8% (4)	17.6% (9)	**0.017**
Expressive	6.1% (6)	5.8% (6)	33.3% (17)	**<0.001**
Written	9.2% (9)	13.5% (14)	19.6% (10)	0.198
Daily Living Skills	5.1% (5)	10.6% (11)	17.6% (9)	**0.049**
Personal	14.3% (14)	15.4% (16)	27.5% (14)	0.103
Domestic	4.1% (4)	4.8% (5)	15.7% (8)	**0.016**
Community	6.1% (6)	10.6% (11)	25.5% (13)	**0.002**
Socialization	5.1% (5)	4.8% (5)	21.6% (11)	**<0.001**
Interpersonal	9.2% (9)	5.8% (6)	21.6% (11)	**0.002**
Play	5.1% (5)	3.8% (4)	23.5% (12)	**<0.001**
Coping	12.2% (12)	12.5% (13)	27.5% (14)	**0.029**
Motor Skills	8.2% (8)	7.7% (8)	31.4% (16)	**<0.001**
Gross	13.3% (13)	6.7% (7)	33.3% (17)	**<0.001**
Fine	10.2% (10)	8.7% (9)	23.5% (12)	**0.022**

Unlike carbamazepine and lamotrigine, prenatal valproate exposure was associated with adaptive behaviour impairments with specific deficits in socialization and motor function, along with a relative weakness in communication. Increasing valproate dose was associated with a decline in adaptive functioning. This finding of a linear dose-dependent teratogenic effect suggests that valproate should be avoided at any dose during pregnancy.

However, some women with epilepsy controlled only by valproate will decide, in consultation with their provider, that the benefits of continuing valproate during pregnancy outweigh the fetal risks. Faced with difficult choices, clinicians should be supportive as these patients consider their options.

3.3.7 Wood et al. 2015 prospective autism study [18]

The association between autism spectrum disorders (ASDs) and prenatal anticonvulsant exposure using a comprehensive, blinded assessment using a validated instrument for autism within a well-characterized prospective cohort has not been conducted. Therefore, the authors conducted a prospective cohort study in children exposed to anticonvulsants during pregnancy, with all assessments conducted by examiners who were blinded to drug-exposure status.

Participants were 105 Australian children aged 6–8 years who were recruited via the Australian Pregnancy Register for Women on Antiepileptic Medication (Table 32). Maternal epilepsy, pregnancy, and medical history data were obtained prospectively. Autism traits were assessed using the Childhood Autism Rating Scale (CARS).

Table 32: Maternal characteristics by drug-exposure group

	Maternal IQ (mean [SD]) (range)	Age at seizure onset (years)	Epilepsy onset type (generalized/partial)	Seizures during pregnancy (no/yes)	Pregnancy duration (weeks)	Child IQ
VPA (mono) (N = 26)	105.9 (12.8) 83–129	15.6 (6.6) 5–31	21G/5P	20N/6Y	39.4 (1.8) 34–42	95.8 (13.3) 66–117
VPA (poly) (N = 15)	91.7 (14.8) 65–120	11.4 (7.5) 1–28	11G/4P	3N/12Y	39.3 (3.1) 29–41	81.0 (17.5) 40–103
CBZ (mono) (N = 34)	108.7 (12.3) 81–129	16.8(10.1) 0–32	7G/23P/4UK	22N/12Y	39.3 (1.4) 36–41	100.7 (14.3) 71–126
"Other"						
Non–VPA poly (N = 19)	102.3 (14.3) 72–123	12.9 (7.4) 0.5–28	5G/13P/1UK	9N/10Y	39.4 (1.0) 38–41	93.8 (10.6) 72–110
LTG mono (N = 9)	109.3 (8.1) 99–119	23.3 (10.3) 1–36	2G/7P	4N/5Y	39.8 (1.7) 38–42	105.1 (5.7) 95–115
Other mono[a] (N = 2)	109.5 (38.9) 109–110	16.0 (8.5) 10–22	2P	1N/1Y	38.5 (0.7) 38–39	96.0 (32.5) 73–119

VPA, valproate; LTG, lamotrigine; CBZ, carbamazepine.
[a]One each topiramate, gabapentin.

Table 33: Rates of elevated CARS scores

	CARS >30	CARS 27–29	Total
Valproate (monotherapy)	1/26	1/26	2/26
	3.8%	3.8%	7.7%
Valproate (polytherapy)	6/15	1/15	7/15
	40.0%	6.7%	46.7%
Carbamazepine (monotherapy)	1/34	1/34	2/34
	2.9%	2.9%	5.9%
Other (mono/polytherapy)	0/30	0/30	0/30
	0.0%	0.0%	0.0%
Total	8/105	3/105	11/105
	7.6%	2.9%	10.5%

Eleven children (10.5%) had elevated CARS scores (Table 33). Two were exposed to valproate monotherapy (2/26; 7.7%), two to carbamazepine monotherapy (2/34; 5.9%), and seven to valproate in poly-therapy (7/15; 46.7%) Table 34.

Linear regression analysis showed that the mean valproate dose during pregnancy was a significant predictor of CARS scores after controlling for poly-therapy, mean carbamazepine dose, folic acid use, seizures during pregnancy, tobacco and marijuana use, maternal intelligence quotient, and socioeconomic status. First trimester folic acid supplementation and marijuana use were also significant predictors of CARS scores (Table 35).

CARS scores were not elevated in children exposed to poly-therapy without valproate, suggesting that valproate, or valproate dose, rather than poly-therapy per se is the critical determinant of the relationship, an observation that requires verification in future studies. The observation of a dose–response relationship within those exposed to valproate in monotherapy suggests a role for valproate in ASD risk.

In this cohort, the proportion of children exposed to carbamazepine monotherapy with elevated scores (5.9%) was higher than the general population, and at a level similar to that of valproate monotherapy.

Table 34: maternal pregnancy history for children with autism spectrum disorders or autistic traits

Case	ASD details	Child IQ	Antiepileptic drug(s)	Daily dose (range across pregnancy)[a]	Other drug(s)	Folic acid[b]	Family history of ASD
1	Autism[c] (CARS = 35)	66	Valproate	3,000 mg	Tobacco (25 cigarettes/day) Marijuana (3 joints/week) Alcohol (2–5 units/day until 12 weeks)	500 µg daily AC	No
2	Autism[c] (CARS = 32.5)	78	Valproate Levetiracetam	1,200 mg 2,000 mg	Tobacco (>30 cigarettes/day) Alcohol (<1 unit/day)	400 mcg daily BC	No
3	Autism[c] (CARS = 33)	82	Carbamazepine	600–800 mg	Paroxetine (dose not specified; until 12 weeks)	None	No
4	PDD-NOS[c] (CARS = 38.5)	61	Valproate Clonazepam	2,500 mg 0.5 mg	None	10 mg daily BC	No
5	CARS = 50; Intellectual and language delay; Socially unresponsive	40	Clonazepam Valproate	0.5 mg (until 21 weeks) 200–400 mg (from 21 weeks)	Tobacco (<10 cigarettes/day) Marijuana (3 joints/day until 12 weeks)	5 mg daily BC	No
6[d]	CARS = 37; Intellectual and language delay; Social difficulties	80	Valproate Lamotrigine	3,000 mg 100 mg	None	None	Sibling (Case 7)
7[d]	CARS = 30; Intellectual and language delay; Social difficulties	64	Valproate Lamotrigine Ethosuximide	2,500–3,000 mg 50–200 mg 500 mg (until 4 weeks)	None	5 mg daily BC	Sibling (Case 6)
8	CARS = 34.5; Intellectual and language delay; Social difficulties	67	Valproate Lamotrigine	1,000 mg 400 mg (until 12 weeks)	Alcohol (<1 unit/week)	5 mg daily BC	Sibling with similar problems[d]
9	CARS = 29; Language delay; Social difficulties	92	Lamotrigine Valproate	400 mg 300 mg (from 29 weeks)	None	5 mg daily BC	Sibling with autism[e]
10	CARS = 28; Language delay; Social difficulties	75	Valproate	1,000–1,500 mg	Diclofenac potassium (irregular from 28 weeks)	500 mcg daily AC	No
11	CARS = 27.5; ADHD[c]; Learning and social difficulties	96	Carbamazepine	1,200 mg	None	5 mg daily BC	Sibling with Asperger's[e]

[a]Where one value is given, the dose was unchanged across pregnancy.
[b]AC, commenced after conception; BC, commenced before conception.
[c]Previously diagnosed.
[d]Cases 6 and 7 were siblings.
[e]By parental report; child was not seen because they were outside the study age range. All three siblings were also AED-exposed.

Nevertheless, children exposed to poly-therapy without valproate were most often exposed to carbamazepine and yet did not show elevated rates of autistic traits, and carbamazepine dose was unrelated to CARS scores. Thus, this data should be interpreted with caution and additional studies are required before changes in practice with regard to carbamazepine in pregnant women should be considered.

Table 35: Predictors of CARS scores in linear regression

Variable	B coefficient (std. error)	t (p)
Mean valproate dose	0.002 (0.001)	3.20 (0.002)
Folic acid first trimester	−8.631 (2.830)	−3.05 (0.003)
Marijuana use	14.844 (2.88)	5.16 (<0.001)
Mean carbamazepine dose	0.000 (0.001)	−0.07 (0.945)
Polytherapy	1.727 (1.126)	1.53 (0.128)
Seizure(s) during pregnancy	0.963 (1.013)	0.95 (0.345)
Maternal IQ	0.000 (0.044)	0.007 (0.994)
Socioeconomic status	−0.014 (0.027)	−0.52 (0.607)
Constant	25.831 (5.007)	5.16 (<0.001)

The authors concluded that there was an elevated rate of autism traits across the sample. The most important determinant of association with autistic traits was higher doses of sodium valproate exposure.

Comment

It should also be noted that cannabis use was a bigger factor for predicting autism traits than sodium valproate use (Table 35). Given the interest in using cannabis in patients with refractory epilepsy this concern should be monitored.

3.3.8 Inoyama and Meador 2015 review of cognitive impairment [19]

There have been numerous animal studies demonstrating poor behavioural, cognitive, and motor functioning in offspring that were prenatally exposed to anti-epileptic drugs. On the cellular level, several groups have demonstrated increased apoptosis and impairment of neurogenesis and synaptogenesis with some AEDs. The effects were dose dependent and were found to occur predominantly during a specific phase of development, between postnatal days 0 to 14, through a mechanism hypothesized to be due to impaired signalling of cell survival pathways.

It was not until years later in 2000 that the question of whether the presence of maternal epilepsy itself causes cognitive dysfunction was systematically addressed, when Holmes et al. published results of a larger cohort of child-mother pairs comparing those without maternal epilepsy and those with a history of maternal epilepsy, excluding all who had taken AEDs during pregnancy or had tonic-clonic seizures while pregnant. Testing was performed to evaluate the intelligence of children ages 6–16 years and both parents, and there was no difference in scores between the groups, indicating that the presence of maternal epilepsy itself was not a risk factor for poor cognitive outcomes in the offspring.

The Neurodevelopmental Effects of Antiepileptic Drug (NEAD) study group performed a multi-centre, prospective study controlling for multiple potentially confounding variables. Their first report on cognitive outcomes evaluated children at 3 years of age, and found children with prenatal exposure to valproate had a reduction in mean IQ score of 9 points compared to lamotrigine, 7 points compared to phenytoin, and 6 points compared to carbamazepine, with those exposed to higher valproate dosages faring worse. Follow-up evaluations at 4.5 years and at 6 years of age demonstrated persistently worse cognitive outcomes in the valproate treated group, not only for IQ but also other measures such as verbal and memory abilities compared to the other monotherapy exposure groups. Further, children exposed to valproate had significantly fewer right handers and lower verbal than non-verbal index scores suggesting the possibility that valproate may affect normal development of cerebral lateralization.

Most studies conducted up to the 1990s lacked evaluation of the mother's IQ, which has been shown to be strongly correlated with the intelligence of her children. A retrospective study by Adab et al. took this into account and assessed 249 children between 6 to 16 years of age and found lower verbal IQs in children with prenatal exposure to valproate. Performance IQ, however, was not

affected even with valproate exposure. In a prospective study with data on maternal IQ, mothers with epilepsy who were on valproate had lower IQ scores and lower education levels than mothers with epilepsy on carbamazepine monotherapy or not on AEDs. However, after controlling for maternal IQ, there was no difference in child IQ amongst the groups, which could either be due to small sample size (total of 39 children) or other inherent differences in the valproate treated group. In contrast, the NEAD study found reduced IQ for children exposed to valproate even after control for maternal IQ, the IQ of children exposed to valproate did not correlate with their mothers' IQ suggesting that fetal valproate exposure disrupts this normal relationship.

Evaluation of prenatal AED exposure in children revealed that 8.9% exposed to valproate and 2.5% exposed to carbamazepine met diagnostic criteria for ASD. A recent large population study from Norway reported that fetal valproate exposure was associated with an increase in autistic spectrum disorder and autism.

There have been inconsistent results as to whether maternal seizures affect intellectual functioning of the offspring. Lower verbal IQ scores were found in children exposed to 5 or more maternal tonic-clonic seizures *in utero*. In contrast, other studies have shown no such correlation. Data from the other studies demonstrated no effect of exposure to maternal seizures *in utero* in children evaluated at 24 months of age, but did find poorer outcomes in language comprehension as well as gross motor skills, personal and social skills, hand and eye coordination, and performance skills during evaluations at 36–54 months of age.

There are numerous possible reasons why studies have found inconsistent results for the cognitive effects of prenatal AED exposure. Various methodologies, including demographic differences in the sampled populations, age at which testing was performed, the types of cognitive tests utilized, and lack of control for confounding variables are at least in part responsible for the variability of results. Confounding factors include maternal IQ and education, which have been found to be closely correlated with child IQ, but were not considered in most studies prior to 2000. In addition, maternal cognitive test scores may also be lowered due to the cognitive side effects of epilepsy and AEDs, further complicating interpretation.

The long term consequences of AED exposure during early infancy on cognitive effects are also not established and require attention. With animal data demonstrating impaired outcomes with AED exposure during the immediate postnatal period, which largely corresponds with a portion of the third trimester and neonatal period in humans, it is highly plausible that the deleterious effects of in utero AED exposure translate to neonatal exposure as well.

3.3.9 Gerard and Meador 2015 — review of behaviour problems [20]

Of all the AEDs, valproate has been most clearly associated with cognitive and behavioural teratogenesis across several human studies. When compared with controls, standardized norms and children exposed to other AEDs, children exposed to valproate *in utero* have been shown to have a delay in achieving developmental milestones and lower IQ scores with particular weaknesses in verbal skills. Valproate-exposed children are also more likely to demonstrate poor adaptive skills and are at an increased risk for neurodevelopmental disorders such as attention- deficit hyperactivity disorder, autism, and autism spectrum disorders.

A relationship between higher doses of valproate and worse developmental outcomes was also suggested in the Australian cohort as well as the Neurodevelopmental Effects of Antiepileptic Drug study. First-trimester valproate dose was significantly correlated with poorer core language scores in the school-age Australian children even when controlling for maternal IQ. In the NEAD study, higher standardized doses of valproate were correlated with lower scores for intelligence measures as well as memory and executive function. While this dose relationship supports the conclusion that valproate can cause neurodevelopmental toxicity, it is not clear that there are "safe" doses of

valproate below which human cognitive teratogenesis does not occur. Further prospective data incorporating valproate levels are needed to address this important point.

In addition to poorer cognitive outcomes, *in utero* valproate exposure has also been associated with impaired behavioural outcomes. A small population-based study conducted in Aberdeen, Scotland reported elevated rates of autism and ASD in children prenatally exposed to valproate monotherapy. In a population based study from Demark, school-age children who were born to mothers prescribed valproate monotherapy during pregnancy had a significantly increased risk of receiving a formal diagnosis of autism or ASD according the national psychiatric register. The absolute risk in the valproate exposed cohort was 2.5% for autism and 4.42% for ASD compared with 0.48 and 1.53% in the general population.

Studies of carbamazepine's effect on cognitive development have been conflicting. Many have found no effect of carbamazepine on cognitive development or academic achievement when compared with controls, other studies, however, did report increased rates of developmental delay in children exposed to carbamazepine.

In summary, it is clear that carbamazepine poses less of a risk for cognitive and behavioural teratogenesis compared with valproate, and is comparable to healthy controls. However, whether certain individuals or behavioural domains are particularly susceptible to carbamazepine exposure needs further study. The authors provided a summary of recent relevant studies (Tables 36 and 37)

Table 36: Antiepileptic drug exposure and cognitive development: Recent studies

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Baker et al (2014)[17]	UK LMNG: prospective cohort with antenatal recruitment from antenatal clinics	6.2 y (6–6.8 y)	CBZ = 50 LTG = 29 VPA (< 800 mg) = 21 (> 800 mg) = 30 VPA PolyTx = 19 Other PolyTx = 11 No AEDs = 25 Other AEDs = 13	Yes *n* = 210	DAS Need for IEP	Yes	VPA > 800 mg/d c/w controls: ↓ FSIQ (9.7 points) ↑ Risk of FSIQ < 85 (RR = 8) ↑ Need for IEP (RR = 8) VPA > 800 mg/d, c/w LTG, CBZ: ↓ FSIQ, nonverbal and spatial IQ, ↓ Verbal IQ c/w LTG only VPA < 800 mg/d c/w controls: No difference in mean FSIQ or FSIQ < 85 ↓ Verbal IQ ↑ Need for IEP (RR = 6) VPA < 800 mg/d c/w LTG, CBZ: No difference in FSIQ, verbal or spatial IQ ↓ Mean nonverbal IQ c/w CBZ only CBZ c/w controls: No difference in mean FSIQ ↑ Risk of FSIQ < 85 (RR = 3.5), ↓ Verbal IQ (4.6 pts) No difference in IEP LTG c/w controls: No difference in IQ scores or IEP PolyTx c/w controls: VPA PolyTx—↓ FSIQ (6.4 points) Other PolyTx—No change in IQ scores	VPA use strongly associated with IGE and CBZ with LRE making it difficult to independently assess effects but more of variance attributed to AED exposure than epilepsy type
Cummings et al (2011)[51]	Ireland WWE: UK epilepsy and pregnancy register (Irish subjects only) Controls: Child Health System Database	Subjects: 2.9 y (0.5–7.5 y) Controls: 4.34 y (1.1–6.5 y)	CBZ = 49 LTG = 35 VPA = 58	Yes *n* = 44	BSID GMDS	No	VPA c/w controls: ↑ Risk of delayed performance (40 vs. 5%) CBZ c/w controls: ↑ Risk of delayed performance (20 vs. 5%) LTG c/w controls: No increased risk of delayed performance	Antenatal identification of subjects but postnatal recruitment; recruitment rates: 58% exposed 15% controls No maternal IQ; VPA mothers had lower educational achievement Control group older than exposed groups

Meador et al (2013)[20]	U. S. and UK NEAD study: prospective cohort with antenatal recruitment	6.2 y (6–7.25 y)	CBZ = 61 LTG = 74 PHT = 40 VPA = 49	No	BRIEF CMS DAS NEPSY DTVMI One-word picture vocabulary	Yes	FSIQ and subscores: CBZ = LTG = PHT VPA < CBZ, LTG, PHT VPA c/w CBZ, LTG, PHT: ↓ FSIQ and verbal IQ ↓ Memory scores, ↓ Nonverbal IQ c/w LTG only ↓ Executive index c/w LTG only VPA > 1,000 mg/d c/w < 1,000 mg/d: ↓ Verbal and nonverbal IQ, ↓ General memory and executive index scores	Included 46 mother–child pairs from Baker et al,[17] No control group
Nadebaum et al (2011)[16]	Australia Australian register for women with epilepsy and allied disorders	7.4 y (6–8 y)	CBZ = 34 LTG = 9 VPA = 23 Other = 2 VPA PolyTx = 15 Other PolyTx = 19	No	CELF-4	Yes	Language scores: VPA PolyTx < VPA < LTG CBZ = LTG = Other PolyTx = expected norm VPA dose in first trimester negatively correlated with language scores VPA PolyTx c/w expected norm: ↓ Language scores ↑ Risk language score < 85 VPA PolyTx c/w CBZ, LTG, VPA: ↓ Language scores c/w LTG and VPA only	Antenatal identification of subjects but postnatal recruitment; recruitment rate: 83% No control group; standardized test norms used for comparison LTG group small
Nadebaum et al (2011)[29]	Australia Australian register for women with epilepsy and allied disorders	7.4 y (6–8 y)	VPA = 23 Other = 2 VPA PolyTx = 15 Other PolyTx = 19	No	WISC-IV	Yes	VPA c/w expected norms ↓ VCI, WM ↑ Risks of IQ < 80 (17.3 vs. 8.9%) VPA dose inversely related to VCI VPA PolyTx c/w expected norms ↓ VCI, WM, PS ↑ Risk of IQ < 80 (40 vs. 8.9%) Other PolyTx c/w expected norms ↓ VCI, WM ↑ Risk of IQ < 80 (15.8 vs. 8.9%)	Same cohort as above

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Rihtman et al (2012)[60]	Israel Exposed: Teratogen information service Controls: Convenience sample	4 y (3–5.6 y)	TPM = 9	Yes *n* = 18	Beery DCDQ M-Fun SB5	No	TPM c/w controls: ↓ General IQ, VIQ, nonverbal IQ ↓ WM, quantitative and fluid reasoning ↓ Visual perception, motor scores	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates not reported Small exposed group; 3/9 subjects exposed in first-trimester only No assessment maternal IQ or education
Rihtman et al (2013)[52]	Israel Exposed: Teratogen information service Controls: Convenience sample	LTG: 3.5 y VPA: 4.3 y Controls 5 y (3–7 y)	LTG = 42 VPA = 30	Yes *n* = 52	Beery DCDQ M-Fun SB5 SP, SSP	No	General IQ and subscores: VPA = LTG = controls VPA c/w controls: No difference in IQ,↓ motor and sensory scores LTG c/w controls: ↓ Visual perception, ↓ motor, and sensory scores VPA c/w LTG No differences on any scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 36% VPA 50% LTG No maternal IQ; educational achievement: LTG < VPA < controls Control group older
Shallcross et al (2014)[18]	UK WWE: UK epilepsy and pregnancy register Controls: LMNG	3.5 y (3–4.5 y)	LEV = 53 VPA = 44	Yes *n* = 131	GMDS Reynell	Yes	VPA c/w controls, ↓ motor, and personal skills ↓ Comprehensive language score VPA c/w LEV ↓ Gross motor skills (15.8 points) LEV c/w controls No difference in any tested scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 35% VPA 83% LEV

Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2nd ed; AED, antiepileptic drug; ASD, autism spectrum disorder; ASQ, ages and stages questionnaire; BASC, behavior assessment system for children; Beery, Beery–Buktenica Developmental Test of Visual-Motor Integration 5th ed; BRIEF, behavior rating inventory of executive function; BSID, Bayley scales of infant development; c/w, compared with; CBZ, carbamazepine; CELF-4, Clinical Evaluation of Language Fundamentals 4th ed; CMS, children's memory scale; Conners', Conners' rating scales–revised; CZP, clonazepam; DAS, differential ability scales; DCDQ, developmental coordination questionnaire; DTVMI, developmental test of visual motor integration; ESAT, early screening of autistic traits questionnaire; FSIQ, full-scale intelligence quotient; GMDS, Griffiths mental development scales; IEP, individual educational plan; IGE, idiopathic generalized epilepsy; IQ, intelligence quotient; LMNG, Liverpool and Manchester Neurodevelopmental Group; LRE, localization-related epilepsy; LTG, lamotrigine; MCHAT, modified checklist of autism in toddlers; M-FUN, Miller function and participation scales; MoBA, the Norwegian mother and child cohort; NEAD, neurodevelopmental effects of antiepileptic drugs; NEPSY, developmental neuropsychological assessment; Other PolyTx, polytherapy without valproic acid; Oxc, oxcarbazepine; PHT, phenytoin; PS, processing speed; PSI-III, Parent Stress Index 3rd ed; Reynell, Reynell language development scale; RR, relative risk; SB5, Stanford–Binet Intelligence Scales 5th ed; SCQ, social communication questionnaire; SP, sensory profile; SSP, short sensory profile; TPM, topiramate; UK, United Kingdom; U.S., United States; VCI, verbal comprehension index; VPA PolyTx, polytherapy including valproic acid; VPA, valproic acid; WASI, Wechsler abbreviated score of intelligence; WISC IV, Wechsler Intelligence Scale for Children 4th ed; WM, working memory; WWE, women with epilepsy.

Rats exposed to several AEDs including benzodiazepines, lacosamide, lamotrigine, phenobarbital, valproate, and vigabatrin either *in utero* or in the early postnatal period exhibited behavioural abnormalities compared with unexposed controls. Valproate exposure has been used to create a rat model of autism.

Lamotrigine or valproate treatment of pregnant rats during embryogenesis was associated with hippocampal or cortical dysplasias in the offspring, which is presumably due to abnormal neuronal migration. AED exposure may also lead to aberrant neurogenesis. Rats treated with gamma-aminobutyric acid (GABA) agonists such as clonazepam, diazepam, or phenobarbital in the early

postnatal period demonstrated decreased proliferation of new neurons in the dentate gyrus of the hippocampus. Magnetic resonance imaging studies in humans have also suggested that aberrant neuronal migration is associated with AED exposure.

In rats, early postnatal exposure to therapeutic doses of clonazepam, diazepam, phenytoin, phenobarbital, valproate, and vigabatrin can cause dose-dependent widespread apoptosis. The apoptotic effects of AEDs on the developing brain are very similar to those seen in rat models of fetal alcohol syndrome.

In addition to affecting the creation and removal of neurons, antiepileptic drugs also, appear to affect the connections between neurons. For example, in the rat model of autism, rat pups exposed to valproate during embryogenesis were found to have an increased number of cortical to cortical connections but each of these connections was less efficient.

Genetic or more specifically, epigenetic mechanisms likely play an important role in AED teratogenesis, though to date this concept has been explored by only a few studies. In a zebrafish model, embryos exposed to valproate had decreased micro-RNA expression. MicroRNA are small noncoding components of DNA that regulate transcription of messenger RNA and hence play an important role in development.

Table 37: Anti-epileptic drug exposure and behavioural development: Recent studies

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Bromley et al (2013)[28]	UK LMNG: prospective cohort with antenatal recruitment from antenatal clinics	6.2 y (6–6.8 y)	CBZ = 50 LTG = 30 VPA = 50 VPA PolyTx = 20 Other PolyTx = 11 No AEDs = 26 Other AEDs = 14	Yes *n* = 214	Diagnosis of NDD NDD = ADHD or ASD or dyspraxia	Yes	VPA c/w controls: ↑ Risk of NDD (12 vs. 1.87%) VPA PolyTx c/w controls: ↑ Risk of NDD (15 vs. 1.87%) CBZ, LTG c/w controls No difference in risk of NDD (CBZ 2%, LTG 6.7 vs. 1.87%) Other PolyTx, no AEDs c/w controls No difference in risk of NDD (Other PolyTx 9%, No AEDs 0 vs. 1.87%)	NDD were not analyzed individually due to small numbers Community specialist making NDD diagnosis not blinded
Cohen et al (2013)[26]	U. S. + UK NEAD study: prospective cohort with antenatal recruitment	6 y Mean and range similar to Meador et al[20]	CBZ = 53 LTG = 63 PHT = 31 VPA = 45	No	ABAS-II BASC PSHII	Yes	ABAS-II general adaptive scores: CBZ = LTG = PHT VPA < LTG, PHT VPA c/w CBZ, LTG, PHT: ↓ Adaptive scores c/w LTG, PHT only ↑ Atypical behavior c/w LTG,PHT only ↑ Inattention c/w LTG, PHT only Adaptive score inversely related to VPA and PHT dose VPA c/w standard norm: ↑ Risk of ADHD based on combined parent and teacher assessment (21 vs. 75%)	Included 46 mother-child pairs from Bromley et al,[28] No control group; standardized norms used for ADHD assessment Parental assessments introduce possible bias
Christensen et al (2014)[14]	Denmark Population study: Civil registers of births and psychiatric diagnoses	8.84 y (4–14 y)	CBZ = 386 CZP = 269 LTG = 647 OXC = 321 VPA = 388	CBZ = 386 CZP = 269 LTG = 647 OXC = 321 VPA = 388	Diagnosis of autism or ASD	No	VPA c/w controls: ↑ Risk autism (2.5 vs. 0.48%) ↑ Risk ASD (4.42 vs. 1.48%) VPA > 750 mg/d c/w < 750 mg/d No difference in risk of autism or ASD CBZ, CZP, LTG, OXC c/w controls No difference in risk of autism or ASD	Exposure databased on filled prescription Controlled for parental psychiatric disorders Community specialist making diagnoses not blinded No difference if VPA prescribed for epilepsy or other diagnosis

Rihtman et al (2012)[60]	Israel Exposed: Teratogen information service Controls: Convenience sample	4 y (3–5.6 y)	4 y (3–5.6 y)	Yes $n = 18$	BRIEF Conners'	No	TPM c/w controls: ↑ Parent reported inattention/cognitive problems ↑ Parent-reported perfectionism No difference in teacher ratings	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates not reported Small exposed group; 3/9 subjects exposed in first trimester only
Rihtman et al (2013)[52]	Israel Exposed: Teratogen information service Controls: Convenience sample	LTG 3.5 y VPA 4.3 y Controls 5 y (3–7 y)	LTG = 42 VPA = 30	Yes $n = 52$	BRIEF Conners'	No	VPA c/w controls: ↓ Parent-reported executive function ↑ ADHD, Connors' global index No difference in teacher-reported measures LTG c/w controls: No difference in parent or teacher measures VPA c/w LTG No differences on any scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 36% VPA 50% LTG No maternal IQ; educational achievement: LTG < VPA < controls Control group older
Veiby et al (2013)[12]	Norway MoBA: Prospective cohort with antenatal recruitment	1.5 and 3 y	Mothers with epilepsy: (1.5 y/3 y) CBZ = 41/31 LT = 65/44 VPA = 25/19 PolyTx = 26/25 No AED = 221/154 Fathers with epilepsy: (1.5 y/3 y) AED = 147/110 No AED = 216/173	Yes $n = 107,597$	ASQ ESAT MCHAT MoBA checklist for ADHD Sentence complexity SCQ	No	VPA c/w controls ↓ Gross motor at 1.5 y ↓ Language at 3 y CBZ c/w controls ↓ Fine motor at 1.5 y ↓ Social skills at 3 y ↑ Aggressive symptoms at 3 y LTG c/w controls ↑ Autistic traits at 3 y ↓ Language score at 3 y No AEDs c/w controls No difference in any scores Fathers with epilepsy c/w controls ↑ Autistic traits at 1.5 y if father on AEDs ↓ Fine motor at 1.5 y if father not on AEDs No difference in any scores at 3 y	Parent f/u by mail survey. Response rate: 73% at 1.5 y 60% at 3 y Parental assessments introduce possible bias Primary outcome aggregate AED effect. AED exposure associated with increased autistic traits, poor sentence skills, and gross motor skills at 3 y PolyTx not divided by type. PolyTx as a group had poor performance on all scores at 1.5 y but not at 3 y

Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2nd ed; ADHD, attention deficit hyperactivity disorder; AED, antiepileptic drug; ASD, autism spectrum disorder; ASQ, ages and stages questionnaire; BASC, behavior assessment system for children; BRIEF, behavior rating inventory of executive function; c/w, compared with; CBZ, carbamazepine; CZP, clonazepam; ESAT, early screening of autistic traits questionnaire; IQ, intelligence quotient; LMNG, Liverpool and Manchester Neurodevelopmental Group; LTG, lamotrigine; MCHAT, modified checklist of autism in toddlers; MoBA, the Norwegian mother and child cohort; NDD, neurodevelopmental disorders; NEAD, neurodevelopmental effects of antiepileptic drugs; OXC, oxcarbazepine; PHT, phenytoin; PolyTx, polytherapy; PSI-III, Parent Stress Index 3rd ed; SCQ, social communication questionnaire; TPM, topiramate; UK, United Kingdom; U.S., United States; VPA, valproic acid.

Valproate is thought to exert epigenetic effects by interfering with histone acetylation and DNA methylation, two interconnected processes that regulate gene transcription. Duration of AED exposure correlates with global hypomethylation. Methylation patterns did not seem to be affected by the condition for which the mother was taking AEDs (mood disorder versus epilepsy). The exact mechanism by which AEDs alter DNA methylation is not known but it is speculated that alterations in the folate/ homocysteine metabolic pathways, which have been associated with many AEDs including lamotrigine and the enzyme inducing AEDs, may be responsible.

If epigenetic modification is found to mediate AED teratogenesis, it may also be possible to uncover individuals whose genomes are more or less susceptible to these effects. For example, in a population-based study in Aberdeen, Scotland, AED-exposed children with congenital malformations and fetal anticonvulsant syndrome were more likely to be born to mothers with a certain polymorphism of methylene-tetrahydrofolate reductase when compared with AED-exposed children who were unaffected. In the same study, AED-exposed children with neurodevelopmental disorders and/or fetal anticonvulsant syndrome were more likely to have polymorphisms of methionine synthase and methionine synthase reductase at trend levels as compared with the healthy children.

Folic acid supplementation is an example of the kind of intervention that might be able to prevent or reduce the epigenetic effects of AEDs, particularly those that are mediated by the DNA methylation pathway: In animal models, folate is able to prevent DNA hypo-methylation and other metabolic changes associated with valproate exposure.

In the Neurodevelopmental Effects of Antiepileptic Drug study, the mean full scale intelligence quotient (FSIQ) of six-year-old children whose mothers reported periconceptional folic acid use was higher than the mean FSIQ of those who were not exposed to supplementation early in pregnancy, even after controlling for other factors such as maternal IQ.

Several recent studies have demonstrated a relationship between periconceptional folic acid supplementation and higher cognitive and behavioural outcomes in the general population. At this point, there is insufficient evidence to conclude that folic acid supplementation mitigates the

structural or developmental teratogenic effects of AEDs; at best it is likely only one of the necessary targets for intervention. More research in this area is greatly needed.

3.3.10 Ban et al. 2015 effect of taking folic acid [21]

The authors included 258,591 singleton live-born children of mothers aged 15-44 years in 1990-2013 from The Health Improvement Network, a large UK primary care database. All major congenital anomalies according to the European Surveillance of Congenital Anomalies classification were identified.

Absolute risks and adjusted odds ratios (aOR) were calculated comparing children of mothers prescribed AEDs to those without such prescriptions, stratified by folic acid prescriptions around the time of conception (one month before conception to two months post-conception).

Previous literature estimates that the prevalence of congenital anomalies is 2.8% and the prevalence of mothers prescribed AEDs in pregnancy is 0.5%. Based on these numbers, we calculated that at least 76,953 children were needed to detect an OR of 2.0 for the association of congenital anomalies with antenatal AED exposure, with 80% power at a 5% significance level. The required sample size to achieve 80% power at a 5% significance level for system-specific anomalies was much larger (257,105 children were needed for heart anomalies based on our study population's prevalence of 0.8%, 408,514 for limb anomalies based on its prevalence of 0.5%, 509,459 for genital anomalies based on its prevalence of 0.4% and 1,014,199 for nervous system anomalies based on its prevalence of 0.2%). Maternal characteristics are outlined in Table 38.

Table 38: Maternal characteristics for children according to their mothers' prescriptions of antiepileptic medicines in pregnancy

	No AEDs in pregnancy		AEDs in the 1st trimester		AEDs only in the 2nd or 3rd trimester	
	n = 257,153		n = 1,259		n = 179	
	n	%	n	%	n	%
Maternal Age, years						
15–24	50,246	19.54	222	17.63	43	24.02
25–34	152,447	59.28	764	60.68	105	58.66
35–44	54,460	21.18	273	21.68	31	17.32
Body Mass Index (kg/m^2)						
Normal (18.5–24.9)	116,794	58.07	510	50.00	82	59.85
Underweight (<18.5)	8,669	4.31	42	4.12	5	3.65
Overweight (25–29.9)	47,646	23.69	251	24.61	18	13.14
Obese (> = 30)	28,009	13.93	217	21.27	32	23.36
Missing*	56,035	[21.79]	239	[18.98]	42	[23.46]
Maternal smoking						
Non-smokers	164,544	81.10	771	74.93	107	79.85
Smokers	38,346	18.90	258	25.07	27	20.15
Missing*	54,263	[21.10]	230	[18.27]	45	[25.14]
Townsend Deprivation Index						
1 (least deprived)	60,602	25.28	235	20.40	30	17.34
2	47,865	19.96	195	16.93	19	10.98
3	51,148	21.33	231	20.05	31	17.92
4	46,386	19.35	275	23.87	51	29.48
5 (most deprived)	33,769	14.08	216	18.75	42	24.28
Missing*	17,383	[6.76]	107	[8.50]	6	[3.35]
Indication for AED prescriptions						
Epilepsy	—		1,024	81.33	144	80.45
Serious mental illness	—		54	4.29	8	4.47
Non-epileptic neurological conditions[a]	—		202	16.04	25	13.97
Indication unknown	—		139	11.04	26	14.53
Folic acid prescriptions[b]						
None	217,355	84.52	502	39.87	125	69.83
Less than 5mg daily	35,529	13.82	104	8.26	24	13.41
At least 5mg daily	4,135	1.61	653	51.87	30	16.76
Dosage unknown	134	0.05	0	0.00	0	0.00

* Percentages in square brackets were calculated when including missing data;

[a] migraine, neuralgia, neuropathic pain and essential tremor in the year before and or during pregnancy;

[b] prescriptions of folic acid in two weeks before pregnancy or in the first eight weeks of pregnancy; AEDs = antiepileptic drugs

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Congenital anomalies risk was 476/10,000 in children of mothers with first trimester AEDs compared with 269/ 10,000 in those without AEDs equating to an aOR of 1.82, 95% confidence interval 1.30-2.56 (Table 39). The highest system-specific risks were for heart anomalies (198/10,000 and 79/ 10,000 respectively, aOR 2.49,1.47-4.21). Sodium valproate and lamotrigine were both associated with increased risks of any congenital anomalies (aOR 2.63,1.46-4.74 and aOR 2.01,1.12-3.59 respectively) and system-specific risks. Stratification by folic acid supplementation did not show marked reductions in AED-associated risks (eg, for congenital anomalies overall aOR 1.75, 1.01-3.03 in the high dose folic acid group and 1.94, 95%CI 1.21-3.13 in the low dose or no folic acid group). However, the majority of mothers taking AEDs only initiated high dose folic acid from the second month of pregnancy (Figure 20).

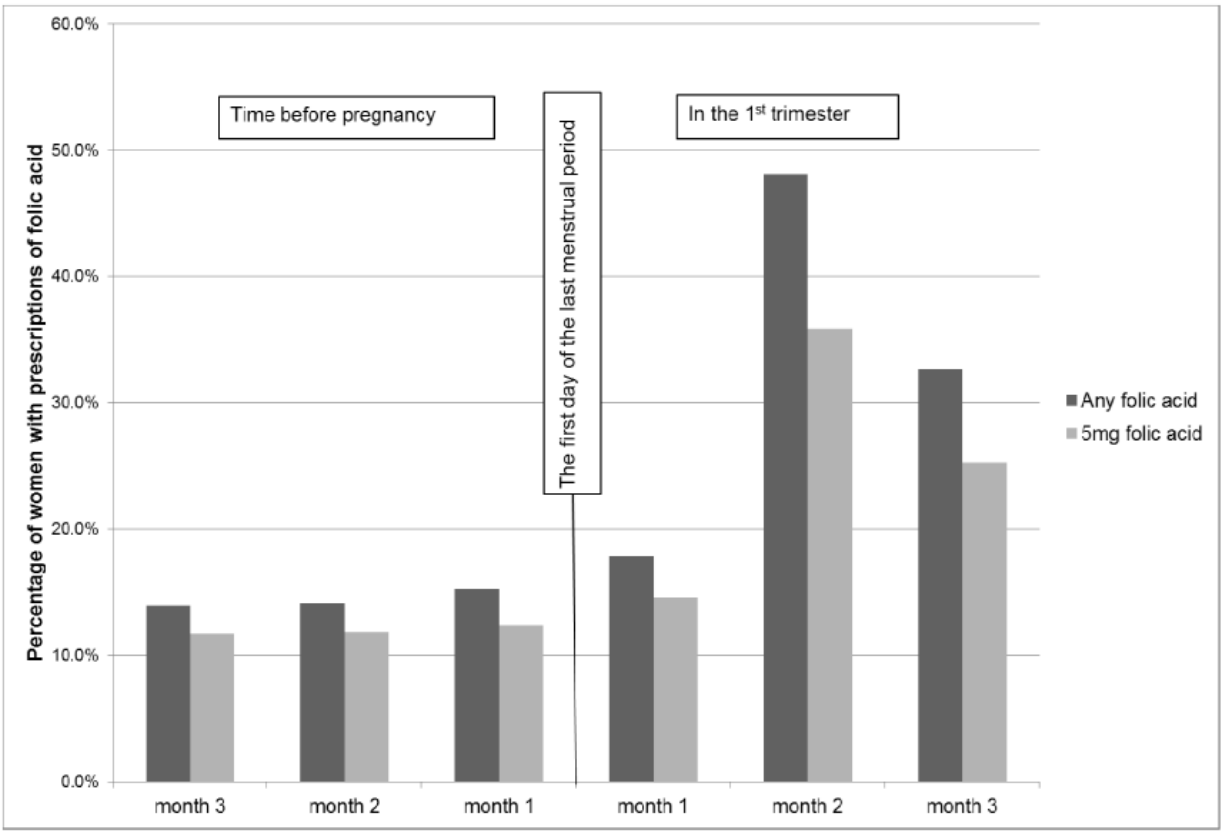

Figure 20: Percentages of women prescribed folic acid among those with first trimester antiepileptic medicine prescriptions

When stratifying the analysis by children of mothers with and without prescriptions of high dose folic acid around early pregnancy, the adjusted ORs were similar (Table 40). When restricting to children of mothers with high dose folic acid throughout the whole periconceptional period, we found that only 66 women with AEDs in the first trimester had high dose folic acid prescribed throughout the whole periconceptional period and less than five had a major congenital anomaly of which none was nervous system anomaly (adjusted OR = 1.52, 95%CI 0.16– 14.16 compared to children of women without AEDs for the overall congenital anomalies risk).

When assessing the effects for individual AEDs, the absolute risks of overall congenital anomaliess were generally highest in children of mothers prescribed valproate (687 per 10,000) and other old AEDs combined (710 per 10,000), followed by the risks in those of mothers prescribed newer drugs (514 per 10,000 for lamotrigine and 369 per 10,000 for other newer drugs combined).

Table 39: Absolute risks (per 10,000 children) of major congenital anomalies in children according to their mothers' prescriptions of antiepileptic medicines in pregnancy

	No AEDs in pregnancy		AEDs in the 1st trimester					
			Overall		Monotherapy		Polytherapy[a]	
	n = 257,153		n = 1,259		n = 1,032		n = 227	
	n	*n/10,000*	n	*n/10,000*	n	*n/10,000*	n	*n/10,000*
Any major anomaly	6,922	*269*	60	*476*	44	*426*	16	*705*
Heart	2,041	*79*	25	*198*	20	*194*	5	*220*
Limb	1,263	*49*	10	*79*	7	*68*	3	*132*
Genital system	1,023	*40*	11	*87*	7	*68*	4	*176*
Nervous system	367	*14*	4	*32*	3	*29*	1	*44*
Other anomalies[b]	2,872	*112*	17	*135*	14	*136*	4	*176*

*Results for 179 children born to women with AEDs only in the 2nd or 3rd trimester, of which 5 had major congenital anomalies, are presented in the text only;

[a] more than one type of antiepileptic drug was prescribed;

[b] All other major congenital anomalies not classified as heart, limb, genital system, or nervous system;

AEDs = antiepileptic drugs

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The pattern was similar for system-specific anomalies (Table 39). Compared with children of mothers without AEDs, the adjusted ORs of overall congenital anomalies were statistically significant for valproate (2.63, 95%CI 1.46–4.73), lamotrigine (2.01, 1.12–3.59) and other older AEDs (2.67, 1.18–6.04) but not for carbamazepine (1.58, 0.86–2.89) and other newer AEDs (1.44, 0.57–3.65).

After stratifying the analysis by folic acid prescriptions, the lamotrigine-associated congenital anomalies risk decreased in the group with high dose folic acid (adjusted OR = 1.60, 95%CI 0.66–3.93), but remained statistically significant in the group with no or low dose folic acid (2.89, 1.29–6.46). However, the confidence intervals of the two ORs overlapped.

Table 40: Odds ratios for the association of major congenital anomalies with antiepileptic medicines in the 1st trimester of pregnancy and risk stratification according to whether high dose (5mg daily) folic acid was prescribed

	AEDs in the 1st trimester							
	Overall				Monotherapy		Polytherapy[a]	
	cOR	95%CI	aOR	95%CI	aOR	95%CI	aOR	95%CI
Overall population	n exposed = 1,259				n exposed = 1,032		n exposed = 227	
Any major anomaly	1.81	1.29–2.55	1.82	1.30–2.56	1.62	1.10–2.42	2.71	1.39–5.29
Heart	2.54	1.51–4.29	2.49	1.47–4.21	2.44	1.36–4.37	2.70	0.84–8.70
Limb	1.62	0.71–3.67	1.66	0.73–3.75	1.42	0.54–3.75	-	
Genital system	2.24	1.02–4.89	2.28	1.04–4.99	1.78	0.67–4.72	-	
Nervous system	-		-		-		-	
Prescriptions of folic acid At least 5mg daily	n exposed = 653				n exposed = 521		n exposed = 132	
Any major anomaly	1.63	0.95–2.80	1.75	1.01–3.03	1.56	0.83–2.92	2.54	0.99–6.54
Heart	2.71	1.19–6.21	3.25	1.41–7.52	3.07	1.25–7.55	-	
Limb	-		-		-		-	
Genital system	2.12	0.63–7.18	2.18	0.61–7.84	-		-	
Nervous system	-		-		-		-	
None/less than 5mg daily	n exposed = 606				n exposed = 511		n exposed = 95	
Any major anomaly	1.96	1.22–3.15	1.94	1.21–3.13	1.71	0.98–2.96	3.22	1.23–8.44
Heart	2.31	1.05–5.08	2.22	1.10–6.92	2.16	0.91–5.16	-	
Limb	2.72	1.09–6.83	2.76	1.12–7.01	2.05	0.64–6.55	-	
Genital system	2.11	0.66–6.69	2.15	0.68–6.82	-		-	
Nervous system	-		-		-		-	

* 134 children whose mothers' were prescribed folic acid had no information on dosage. Empty cells indicate there were fewer than five exposed cases, for which statistical analyses were not performed;

[a] more than one type of antiepileptic drug was prescribed;

cOR = crude odds ratio; aOR = odds ratio adjusted for maternal age, year of childbirth, maternal body mass index, smoking and socioeconomic status; AEDs = antiepileptic drugs; 95%CI = 95% confidence interval

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Table 41: Absolute risks (per 10,000 children) of major congenital anomalies in children according to type of antiepileptic medicine in the 1st trimester of pregnancy

	Individual types of AEDs in the 1st trimester of pregnancy									
	Carbamazepine		Sodium valproate		Other older AEDs[a] combined		Lamotrigine		Other newer AEDs[b] combined	
	n = 450		n = 291		n = 155		n = 389		n = 217	
	n	*n/10,000*	n	*n/10,000*	n	*n/10,000*	n	*n/10,000*	n	*n/10,000*
Any major anomaly	19	*422*	20	*687*	11	*710*	20	*514*	8	*369*
Heart	8	*178*	6	*206*	5	*323*	9	*231*	2	*92*
Limb	2	*44*	5	*172*	1	*65*	4	*103*	0	-
Genital system	5	*111*	4	*137*	3	*194*	2	*51*	3	*138*
Nervous system	2	*44*	3	*103*	0	-	1	*26*	0	-
Other anomalies[c]	5	*111*	4	*137*	4	*258*	5	*129*	4	*184*

[a] phenytoin, clonazepam, clobazam, phenobarbital, ethosuximide, or primidone;
[b] gabapentin, levetiracetam, pregabalin, topiramate, vigabatrin, zonisamide, or lacosamide;
[c] All other major congenital anomalies not classified as heart, limb, genital system, or nervous system;
AEDs = antiepileptic drugs

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The authors concluded that children of mothers with AEDs in the first trimester of pregnancy have a 2-fold increased risk of major congenital anomalies compared to those unexposed. There was no evidence that prescribed high dose folic acid supplementation reduced such AED-associated risks. Although statistical power was limited, prescribing of folic acid too late for it to be effective during the organogenic period or selective prescribing to those with more severe morbidity may explain these findings.

Comments

Folic acid supplementation needs to start at least three months prior to conception (UK recommendation) in order to be effective. Given the results starting to emerge regarding risk being associated with polymorphisms in enzymes associated with folate metabolism other forms of folate other than folic acid may be more effective.

3.3.11 Vajda et al. 2015 untreated epilepsy [22]

The aim of this study was to determine the outcomes in pregnant women with epilepsy not treated with anti-epileptic medicines.

Analysis of data from the Australian Register of AEDs in Pregnancy on 148 women with epilepsy who were not receiving AEDs before and during at least the first trimester of pregnancy (Table 42).

The Register, which has been collecting data since 1999, is estimated to have captured some 8 to 9% of all Australian pregnancies in women with epilepsy. These women initiated their own participation in the Register's database once they had become aware of its existence. All contact between the women and the Register was by means of telephone, with interviews on 4 occasions – at recruitment as early in pregnancy as feasible, at 7 months of gestation, in the post-partum month and, as far as possible, one year after childbirth.

Table 42: Characteristics of the untreated and anti-epileptic drug treated pregnant women with epilepsy and outcomes

	No AEDS	$P<.05$	AEDs	R.R. or Difference	95% C.I.
Number	148		1532		
Mean Age (years)	30.74		30.69	−0.05[a]	−1.02, +1.12
Referral source – neurologist	51.4%		47.9%	1.07	0.91, 1.26
Referral source – other medical practitioner	12.2%		15.9%	0.77	0.49, 1.20
Pregnancy number – 1	46.6%		41.6%	1.12	0.93, 1.34
Pregnancy number – 2	32.4%		29.6%	1.09	0.86, 1.40
Pregnancy number – 3	11.5%		16.1%	0.71	0.45, 1.49
Pregnancy number – 4	6.1%		7.1%	0.85	0.44, 1.65
Pregnancy number – >4	3.4%		5.4%	0.62	0.25, 1.49
Pregnancies 1 and 2 combined	79.1%	>	73.1%	1.11	1.01,1.21
Assisted fertilisation involved	5.4%		5.8%	0.93	0.43, 1.68
Previous malformed offspring ($N=79,894$)	2.5%		4.8%	0.53	0.13, 2.13
Previous neonatal deaths ($N=79,894$)	1.3%		0.8%	1.62	0.20, 12.97
Epilepsy duration (mean in years)	12.3	<	14.1	−1.80[a]	−3.25, −0.35
Epilepsy type – partial	44.6%		49.0%	0.91	0.76, 1.10
Epilepsy type – generalised	45.9%		42.5%	1.08	0.90, 1.30
Epilepsy type – uncertain	9.5%		8.6%	1.11	0.65, 1.07
AED change before pregnancy	41.9%	>	14.2%	3.03	2.42, 3.79
Preconception folate intake	65.5%	<	70.8%	0.85	0.75, 0.98
Seizures during pregnancy – any	56.1%	>	46.9%	1.20	1.03, 1.39
Seizures during pregnancy – convulsive	24.3%		18.9%	1.29	0.95, 1.74)
Active epilepsy before pregnancy	50.0%		43.6%	1.15	0.97, 1.36
Seizures during pregnancy – any	82.4%		79.1%	1.04	0.93, 1.16
Seizures during pregnancy – convulsive	36.5%		32.8%	1.13	0.81, 1.53
Seizures during birth	2.7%		3.6%	0.75	0.18, 3.12
Inactive epilepsy before pregnancy	50.0%		56.4%	0.89	0.75, 1.05
Seizures during pregnancy – any	29.7%		21.9%	1.36	0.94,1.97
Seizures during pregnancy – convulsive	12.2%		8.2%	1.48	0.77, 2.84
Seizures during birth	3.4%		0.9%	2.92	0.63, 13.50
Malformed foetus	3.4%		7.1%	0.47	0.20, 1.15
Malformed foetus[b]	3.4%		4.5%	0.74	0.30, 1.84
Malformed foetus[c]	3.4%	<	12.1%	0.28	0.11, 0.68

[a] A difference, not a R.R. value.
[b] Pregnancies exposed to VPA and TPM excluded.
[c] Pregnancies exposed to VPA or TPM.

Within the 148 pregnancies not treated with AEDs at the time of conception a number of features, mainly concerning seizure activity, were compared between the women whose seizure disorders were active before pregnancy and those whose disorders were inactive (Table 43). The only significant difference between the two groups was a considerably higher rate of seizure occurrence during pregnancy in the women with already active epilepsies at entry into pregnancy (any seizures: 82.4% versus 29.7%; convulsive seizures: 36.5% versus 12.2%).

Seizure control was less likely to be maintained in AED-untreated pregnancies. Whether AED therapy had been ceased in preparation for pregnancy, or had not been employed for long periods before pregnancy, made no statistically significant difference to seizure control outcomes, but those who ceased therapy in preparation for pregnancy were more likely to again be taking AED therapy by term. Fetal malformation rates were reasonably similar in untreated pregnancies, and in treated pregnancies if pregnancies exposed to known AED teratogens (valproate and probably topiramate) were excluded from consideration.

It appeared that the main determinant of the outcome regarding seizure occurrence in anti-epileptic drug-untreated pregnancy was not so much the length of time before pregnancy over which no anti-epileptic drug treatment was taken, but whether the women's epilepsy was active or inactive when they entered pregnancy. If the epilepsy was active, women would probably tend to experience further seizures during pregnancy so that the disadvantages and hazards that they were already experiencing would continue. If the epilepsy prior to pregnancy was inactive, the women seemed to have less risk of having seizures during pregnancy than the women whose pre-pregnancy epilepsy was active. However, the women with inactive epilepsy still had about a 30% risk of seizures in pregnancy. This risk appeared greater, though not statistically significantly so, than the risk of seizures returning in pregnancy in the women with inactive pre-pregnancy epilepsy who continued to take antiepileptic medication in pregnancy.

Table 43: Comparisons between women with active and inactive epilepsies that were not treated with anti-epileptic drugs at least in earlier pregnancy. The likelihood (RR) of various items occurring in the active epilepsy group is expressed relative to that for the women with inactive epilepsies

	Active Epilepsy	$P < .05$	Inactive Epilepsy	R.R or Difference	95% C.I.
Number	74		74		
Mean Age (years)	30.1		31.4	−1.30[a]	−2.85, 0.25
Referral source – neurologist	54.1%		48.6%	1.11	0.81, 1.52
Referral source – other medical	16.2%		8.1%	2.00	0.79, 5.05
Pregnancy numbers – 1 or 2	78.4%		79.7%	0.98	0.83, 1.16
Pre-conception folate intake	59.5%		74.3%	0.80	0.64, 1.01
Epilepsy – partial	47.3%		41.9%	1.13	0.79, 1.62
Epilepsy – generalised	41.9%		50.0%	0.84	0.59, 1.19
Epilepsy – type uncertain	10.8%		8.3%	1.30	0.47, 3.55
Epilepsy duration (mean in years)	10.6	<	14.1	−3.50[a]	−6.54, +0.46
Seizures during pregnancy – any	82.4%	>	29.7%	4.00	2.39, 6.70
Seizures during pregnancy – convulsive	36.5%	>	12.2%	3.00	1.52, 5.93
Seizures during birth	2.7%		2.7%	1.00	0.14, 6.91
Taking AEDs by 7 months	53.1%	>	29.7%	1.79	1.18, 2.72
Taking AEDs by term	55.4%	>	37.8%	1.46	1.03, 2.09
Taking AEDs by term – had seizures	51.2%		57.1.4%	0.90	0.58, 1.39
Foetal Malformations	2.7%		4.1%	0.67	0.11, 3.87

[a] A difference, not a RR

The authors concluded that leaving epilepsy untreated during pregnancy appears disadvantageous from the standpoint of seizure control; it also does not reduce the hazard of fetal malformation unless it avoids valproate or topiramate intake during pregnancy.

3.3.12 Tomson et al. 2015 guidance on epilepsy treatment [3]

A joint Task Force of the Commission on European Affairs of the International League Against Epilepsy and the European Academy of Neurology, reviewed the use of valproate in women following strengthened warnings from the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) of the European Medicines Agency.

To produce these recommendations, the Task Force considered teratogenic risks associated with use of valproate and treatment alternatives, the importance of seizure control and of patient and fetal risks with seizures, and the effectiveness of valproate and treatment alternatives in the treatment of different epilepsies.

Recommendations for the use of valproate in the treatment of epilepsy in girls and women of child bearing potential.

- The choice of treatment for girls and women of childbearing potential should be that of a shared decision between clinician and patient, and be based on a careful risk–benefit assessment of reasonable treatment options for the patient's seizure or epilepsy type.
- Given the risks associated with exposure *in utero*, valproate should be avoided wherever possible as initial treatment of epilepsy in girls and women of child bearing potential.
- Valproate should thus generally not be used for treatment of focal epilepsies, and withdrawal of valproate or switch to treatment alternatives should be considered for women of childbearing potential who are established on treatment with valproate for focal seizures and who are considering pregnancy.
- In cases where valproate is considered the most appropriate option (eg, some idiopathic/genetic generalized epilepsies), every female patient and the parents of a female child must be fully informed of the risks associated with valproate use during pregnancy as well as of the risks and benefits of treatment alternatives.
- When used in girls and women of childbearing potential, valproate should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500–600 mg/day, although, at times, higher doses may be necessary to attain seizure control.
- Women of childbearing potential who are not planning pregnancy and who continue treatment with valproate should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided.

- It is generally not advisable to switch from valproate to another treatment in women who discover that they are pregnant while on valproate.
- Women should be informed about the possibilities and limitations of prenatal screening, which may detect major malformations but cannot identify children whose neurodevelopment will be affected.

The Task force also provided guidance on use of valproate in different clinical situations (Table 44 and 45).

Table 44: Risk-benefit analysis of valproate use and alternative treatment strategies in different clinical situations

Clinical indication	Scenario	Risks	Benefits	Comments
Newly diagnosed epilepsy where valproate is likely more effective than alternative AEDs	Valproate not prescribed unless other treatments failed	• Delayed seizure control • Increased risk of seizures • Adverse psychosocial impact due to lack of seizure control	• Reduction of risk of teratogenicity and neurodevelopmental delay • Less need to switch when pregnancy planned	The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures
	Valproate prescribed as initial treatment in selected patients	• Teratogenicity and risk of neurodevelopmental delay in case of pregnancy • Switch if pregnancy is planned or patient reached an age with childbearing potential	• Highest chance of full seizure control in selected syndromes • Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Female patients with epilepsies for which valproate is particularly effective and who have failed on treatment alternatives	Valproate not prescribed	• Delayed seizure control • Increased risk of seizures • Adverse psychosocial impact due to lack of seizure control	• Reduction of risk of teratogenicity and neurodevelopmental delay • Less need to switch when pregnancy planned	The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures
	Switch from existing treatment to valproate	• Teratogenicity and risk of neurodevelopmental delay in case of pregnancy • Switch if pregnancy is planned or patient reached an age with childbearing potential	• Highest chance of full seizure control in selected syndromes • Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Female patient on valproate not considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	• Seizure relapse with potential consequences (injury, driving license, etc.)	• Avoidance of unnecessary drug treatment • Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Switch of valproate to an alternative treatment	• Seizure relapse in seizure-free patients with potential consequences (injury, driving license, etc.) • Seizure deterioration in patients who are not seizure free • Adverse effects of the new drug • Teratogenicity of the new drug	• Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay • Chance of improved seizure control if suboptimal on valproate	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Unchanged treatment with valproate	• Risk of teratogenicity and neurodevelopmental delay in case of pregnancy	• Avoidance of unnecessary suboptimal seizure control	Requires a proactive approach with reminders of need to reassess treatment in future

Continued

Clinical indication	Scenario	Risks	Benefits	Comments
Female patient taking valproate considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	• Seizure relapse with potential consequences (injury, driving license, etc.)	• Avoidance of unnecessary drug treatment • Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Switch from valproate to an alternative treatment	• Seizure relapse in seizure-free patients with potential consequences (injury, driving license, etc.) • Seizure deterioration in patients who are not seizure free • Adverse effects of the substituted drug, including its possible teratogenicity	• Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay • Chance of improved seizure control if suboptimal on valproate	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Unchanged treatment with valproate	• Risk of teratogenicity and neurodevelopmental delay	• Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Woman already on valproate treatment while pregnant	Withdrawal of valproate	• Maternal and fetal risks of uncontrolled seizures	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	Withdrawal of valproate during pregnancy is unlikely to reduce the risk of malformations Risks outweigh possible benefits
	Switch from valproate to an alternative treatment	• Maternal and fetal risks of uncontrolled seizures • Teratogenicity and risk of valproate-associated neurodevelopmental delay • Teratogenicity of substituted drug and its transient combination with valproate • Adverse effects of the substituted drug	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	No data available on pregnancy outcomes after treatment switches during pregnancy Exchange of valproate during pregnancy is unlikely to reduce the risk of malformations Risks outweigh possible benefits
	Reduction of valproate dose	• Maternal and fetal risks of uncontrolled seizures	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	Reduction of valproate dose during pregnancy unlikely to reduce risk of malformations The magnitude of the benefits depends on dose and potentially present adverse effects

AED, antiepileptic drug; GTCS, generalized tonic-clonic seizure.

Table 45: Specific epilepsy syndrome where valproate may be considered the most appropriate initial treatment

Syndrome	Evidence	Childbearing potential	Comment
Childhood absence epilepsy	Randomized controlled studies[25]	Not affected	Ethosuximide equally effective and better tolerated[25] Self-limiting in childhood in the majority
Juvenile myoclonic epilepsy	Randomized controlled studies	Not affected	Data derived from studies addressing seizure types, not syndromes (see text)
Juvenile absence epilepsy	Randomized controlled studies	Not affected	Data derived from studies addressing absence seizures, not syndromes (see text)
Epilepsy with generalized tonic–clonic seizures alone	Randomized controlled studies	Not affected	Data derived from studies addressing seizure types, not syndromes (see text)
Myoclonic epilepsy in infancy	Observational[52]	Not affected	Self-limiting in childhood
Atypical benign focal epilepsy (atypical evolution of BECTS)	Observational[47]	Not affected	Self-limiting around puberty
Eyelid myoclonia and absences (Jeavons syndrome)	Observational[53]	Not affected	
Epilepsy with myoclonic absences	Observational[47,54]	Reduced	
Epilepsy with myoclonic atonic seizures	Observational[55]	Reduced	Variable course
Epileptic encephalopathy with continuous spike-and-wave waves in sleep (ESES/CSWS), including Landau-Kleffner syndrome	Observational[56]	Reduced	ESES self-limiting around puberty
Progressive myoclonic epilepsies	Observational[57]	Reduced	Valproate contraindicated for some mitochondrial disorders, especially with *POLG* mutation[58]
Dravet syndrome	Observational[59]	Very rare	RCT evidence for stiripentol added to the combination of valproate and clobazam[60]
Lennox-Gastaut syndrome	Observational[47]	Very rare	

BECTS, benign epilepsy with centrotemporal spikes; ESES, electric status epilepticus in sleep; CSWS, continuous spike-waves during sleep; RCT, randomized controlled trial.

3.3.13 Epstein et al. 2015 — guidance on bipolar treatment [23]

Bipolar disorders, including bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified, are serious, chronic psychiatric illnesses characterized by alternating episodes of mania or hypomania and major depression, or mixtures of manic and depressive features. They represent a spectrum of illnesses characterized by frequent relapses, symptom recurrences, and persisting residual symptomatology. Bipolar disorders have major adverse clinical, social, and economic effects that often interfere with the patient's ability to work and function normally in other instrumental life roles and in social relationships. The annual incidence of bipolar disorders ranges from three to ten cases per 100,000 population, with an estimated lifetime prevalence of 3%–7%.

The incidence of bipolar disorders in women peaks from 12 to 30 years of age, (eg, during the primary reproductive years), raising the possibility of considerable bipolar illness burden during pregnancy and the postpartum period.

The treatment of bipolar disorders during pregnancy presents numerous clinical challenges (Tables 46 and 47). Many primary mood stabilizers are associated with increased risk of congenital malformations. However, stopping treatment during pregnancy may increase the risk of bipolar mood-episode relapses. In the last 15 years, there has been increasing antepartum use of atypical antipsychotic drugs, many of which could be viable alternatives to mood stabilizers. However, relatively little is known about the reproductive safety of these agents.

Compared to control mothers, mothers with bipolar disorder were at significantly higher risk of experiencing placental abnormalities, antepartum haemorrhages, and toxicities related to alcohol, tobacco, and illicit-substance use. In a large-scale observational study using the Taiwan National Health Insurance Research Database, a diagnosis of bipolar disorder was associated with significantly higher likelihood of low birth weight, preterm birth, and smallness for gestational age delivery compared with absence of a psychiatric diagnosis

Regardless of treatment status, rates of smoking, overweight, and substance abuse were significantly higher among women with a diagnosis of bipolar disorder compared with control women.

Previous research has also shown that the offspring of women with bipolar disorder have increased rates of neurocognitive and psychiatric impairment. In a cohort study of 117 offspring (ages 4–18 years) of 88 parents with bipolar disorder (high-risk youth) and 171 offspring of parents without a major affective disorder (control youth), high-risk youth had significantly increased rates of affective, anxiety, and disruptive behavioural disorders, memory and attention disturbances, and impaired social functioning than control youth

Finally, uncontrolled or untreated bipolar disorder exposes affected mothers to well-documented behavioural risks that accompany acute manic or depressive relapses. These include increases in impulsive and risky behaviours, unplanned pregnancy, substance use, poor adherence to prenatal care, disruptions in support structures and family functioning, and maternal suicide: a leading cause of perinatal mortality.

Recently published meta-analysis of 68 randomized trials (16,703 subjects) showed that antipsychotic drugs were significantly more effective than mood stabilizers for treating acute mania, and that haloperidol performed the best on an integrated assessment of anti-manic effectiveness These results and the better-known reproductive safety profile of haloperidol compared with many other agents for treating acute mania may increase its appeal for acute treatment of mania during pregnancy, notwithstanding other factors (eg, extrapyramidal side effects, tardive dyskinesia with long-term use, lack of bipolar anti-depressive efficacy, etc) that may limit its usefulness.

Fewer established treatments exist for acute bipolar depression than acute manic or mixed episodes.

Meta-analyses of randomized trials support the effectiveness of quetiapine, an olanzapine–fluoxetine combination, and lamotrigine although patients with severe depression appear to be more likely to benefit from lamotrigine than those with milder depression.

Table 46: Pharmacotherapeutic options for treating cute manic (or mixed) episodes

Drug class/name	Regulatory approval[a,b]	Pregnancy-safety rating (US)[c]	Summary of major reproductive safety concerns
Mood stabilizers			
Lithium	Adults[mono] Youth (aged 12+ years)	D	• Overall MCM rate 2.8% (prospective studies) • Includes low risk of Ebstein's anomaly (one case per 1,000–2,000 births) • Reported cases of neonatal adaptation syndrome; risk may be higher with higher maternal lithium levels • Reported cases of other neonatal complications
Valproate	Adults[mono,*]	D	• Highest MCM rates among all mood stabilizers (5%–11%, based on registry study data); risk may be dose-dependent (maternal daily dose) • Increased MCM risk when combined with other anticonvulsants • Increased risk of adverse neurodevelopmental outcomes • Reported cases of neonatal toxicity syndromes
Carbamazepine	Adults[d,mono,*]	D	• Overall MCM rate 2%–6% based on registry study data • Several adverse neonatal events aside from birth defects reported
Antipsychotics, atypical			
Clozapine	–	B	• MCM risk unclear, very few large-scale studies • Very limited data on reproductive risks associated with individual drugs • FDA safety warning regarding risk of abnormal muscle movements and withdrawal symptoms in neonates • Possible risks of excessive weight gain and gestational diabetes require additional study
Risperidone	Adults[mono,com]	C	
Olanzapine	Adults[mono,com,*]	C	
Quetiapine	Adults[mono,com,*]	C	
Ziprasidone	Adults[mono,*]	C	
Aripiprazole	Adults[mono,com,*]	C	
Asenapine	Adults[mono,com,*]	C	
Antipsychotics, typical	Adults (chlorpromazine only)	C	• Low risk of MCMs, but this is based on very few reports • FDA safety warning regarding risk of abnormal muscle movements and withdrawal symptoms in neonates

A retrospective study, Viguera et al. compared recurrence rates for 42 patients with bipolar I or II disorder during pregnancy or the postpartum period following rapid (over #14 days) or gradual (over 15–30 days) discontinuation of lithium maintenance therapy. Lithium discontinuation commenced within six weeks of the estimated date of conception. A cohort of 59 age-matched non-pregnant women with bipolar disorder who also discontinued lithium treatment served as a control group. Recurrence rates following lithium discontinuation did not differ significantly between pregnant women and non-pregnant controls (52% versus 58%). However, recurrence rates were lower in both groups during the year prior to medication discontinuation (21%).

A subsequent prospective cohort study by the same group compared the risk of recurrence in 89 euthymic women with bipolar I or II disorder who continued mood-stabilizer treatment during pregnancy or discontinued mood stabilizers during the time period beginning six months before and ending 12 weeks after conception. The risk of recurrence during pregnancy was 85.5% for women who discontinued mood stabilizers and 37.0% for those who continued mood-stabilizer treatment. Median time to recurrence was four times shorter and the proportion of weeks ill during pregnancy was five times greater with mood-stabilizer discontinuation compared with continuation of mood stabilizers. Women who discontinued mood stabilizers spent over 40% of pregnancy in an episode of illness compared with 8.8% for those who continued mood stabilizers. Recurrences were predominantly depressed or mixed episodes occurring in the first trimester of pregnancy.

Table 47: Pharmacotherapeutic options for treating acute depressive episodes

Drug class/name	Regulatory approval[a,b]	Pregnancy-safety rating (US)[c]	Summary of major reproductive safety concerns
Mood stabilizers			
Lithium	–	D	• Overall MCM rate 2.8% (prospective studies) • Includes low risk of Ebstein's anomaly (one case per 1,000–2,000 births) • Reported cases of neonatal adaptation syndrome; risk may be higher with higher maternal lithium levels • Reported cases of other neonatal complications
Valproate	–	D	• Highest MCM rates among all mood stabilizers (5% -11%, based on registry study data); risk may be dose-dependent (maternal daily dose) • Increased MCM risk when combined with other anticonvulsants • Increased risk of adverse neurodevelopmental outcomes • Reported cases of neonatal toxicity syndromes
Carbamazepine	–	D	• Overall MCM rate 2% -6% based on registry study data • Several adverse neonatal events aside from birth defects reported
Lamotrigine	–	C	• Unclear if lamotrigine increases risk of MCMs above background rates • Unclear if lamotrigine increases risk of other neonatal adverse events outside of birth defects • No evidence of increased risk of adverse neurodevelopmental outcomes
Antipsychotics, atypical			
Olanzapine	Adults[d]	C	• MCM risk unclear, very few large-scale studies • Very limited data on reproductive risks associated with individual drugs • FDA safety warning regarding risk of abnormal muscle movements and withdrawal symptoms in neonates • Possible risks of excessive weight gain and gestational diabetes require additional study
Quetiapine	Adults[mono]	C	• MCM risk unclear, very few large-scale studies • Very limited data on reproductive risks associated with individual drugs • FDA safety warning regarding risk of abnormal muscle movements and withdrawal symptoms in neonates • Possible risks of excessive weight gain and gestational diabetes require additional study
Lurasidone	Adults[mono,com]	B	• No evidence of teratogenicity in animals; no reproductive safety data in humans • Available only relatively short time for clinical use

A systematic review of information about the risk of major congenital malformations with *in utero* exposure to lithium concluded that lithium should not be considered a major human teratogen based on reports published between 1969 and 2005, and that lithium should be administered to pregnant women if indicated. However, the authors also recommended due caution and supported existing recommendations for performing fetal echocardiography to exclude the possibility of cardiac malformations.

Exposure to lithium late in pregnancy has been associated with development of a neonatal adaptation syndrome characterized by hypotonicity, muscle twitching, respiratory and feeding difficulties, cardiac arrhythmias, cyanosis, poor suck, grasp, and Moro reflexes, and lethargy. The syndrome resolves in 1–2 weeks, and usually without further complication; however, intensive neonatal monitoring and longer hospital stays may be required.

Other neonatal effects have been associated with maternal lithium use during the second and third trimesters that may reflect complications of lithium use in the neonate, rather than toxicity. These include reversible hypothyroidism, nontoxic goiter, nephrogenic diabetes insipidus, and hypoglycaemia.

Based on two systematic reviews of observational studies and case literature, there is no clear evidence of an association between typical or atypical antipsychotic drugs and major congenital malformations. Among the typical antipsychotics, reproductive safety risks are best understood for haloperidol, chlorpromazine, and perphenazine. For example, in a prospective study of 188 pregnancies exposed to haloperidol and 27 to penfluridol, major congenital malformation rates in both exposure groups combined (3.4%) approximated major malformation rates in the general

population, and did not differ statistically in comparison to that of 631 unexposed control pregnancies (3.8%).

Both typical and atypical antipsychotics have been associated with perinatal complications, including extrapyramidal signs, respiratory distress, seizures, feeding difficulties, tachycardia, low blood pressure, and transient neurodevelopmental delay

In a very large population-based retrospective cohort study of 169,338 antipsychotic-exposed and 357,696 -unexposed pregnancies, antipsychotic drug use during pregnancy was associated with an increased risk of gestational diabetes compared with the total population of births, after adjusting for birth order and maternal age, country of birth, cohabitation, smoking, and height (adjusted OR 1.77, 95% CI 1.04–3.03).

There have been very few investigations of possible adverse neurodevelopmental outcomes in children with *in utero* exposure to antipsychotic drugs. In one prospective controlled study Infants with prenatal antipsychotic drug exposure had significantly lower neuromotor-performance scores as measured by the Infant Neurological International Battery, a standardized assessment of posture, muscle tone, reflexes, and motor skills, in comparison with antidepressant-exposed children or children with no psychotropic exposure.

4.0 NEW ZEALAND DATA

4.1 Use in women of child bearing age

The number of community dispensed prescriptions of Epilim for women of child-bearing age is shown in Tables 48 and 49.

Table 48: Data provided by PHARMAC to Medsafe in 2011 for the 2010 calendar year

Age at YE Dec	*Sodium valproate*		*Age at YE Dec*	*Sodium valproate*	
	Female	*Male*		*Female*	*Male*
0	*8*	*9*	*26*	*135*	*164*
1	*14*	*21*	*27*	*122*	*180*
2	*34*	*38*	*28*	*141*	*185*
3	*22*	*41*	*29*	*125*	*185*
4	*39*	*49*	*30*	*142*	*179*
5	*42*	*54*	*31*	*148*	*185*
6	*49*	*58*	*32*	*138*	*172*
7	*49*	*62*	*33*	*158*	*203*
8	*49*	*57*	*34*	*151*	*194*
9	*46*	*65*	*35*	*141*	*222*
10	*42*	*71*	*36*	*223*	*201*
11	*53*	*51*	*37*	*183*	*229*
12	*68*	*62*	*38*	*209*	*247*
13	*50*	*68*	*39*	*234*	*257*
14	*55*	*79*	*40*	*225*	*267*
15	*63*	*80*	*41*	*248*	*267*
16	*76*	*111*	*42*	*245*	*241*
17	*61*	*94*	*43*	*241*	*256*
18	*60*	*131*	*44*	*237*	*270*
19	*112*	*147*	*45*	*227*	*240*
20	*111*	*157*	*46*	*249*	*249*
21	*115*	*135*	*47*	*255*	*237*
22	*118*	*157*	*48*	*265*	*281*
23	*120*	*195*	*49*	*289*	*267*
24	*113*	*186*			
25	*123*	*183*			
Grand Total all ages	***12,826***	***13,670***			

Table 49: Number of community dispensed prescriptions of Epilim for women, 2014 to 2016

Number of female clients under 50 years old dispensed Sodium Valproate, by quarter, gender and age group.
Source: MoH Pharms collection extracted March 2017

Female - only	2014				2015				2016			
Age group	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
0 to 4	127	118	127	120	99	89	99	97	87	81	73	73
5 to 9	149	149	148	147	130	147	150	142	132	136	140	140
10 to 14	193	187	191	205	194	202	180	177	194	184	183	184
15 to 19	310	321	323	324	317	313	326	307	287	297	287	288
20 to 24	421	407	396	382	392	371	372	382	365	360	385	370
25 to 29	457	458	464	450	437	440	435	425	430	404	423	430
30 to 34	558	542	551	547	534	535	530	540	515	503	536	533
35 to 39	838	826	838	833	799	797	817	788	749	727	742	741
40 to 44	918	926	969	982	921	937	940	937	935	966	998	1,002
45 to 49	163	163	169	149	151	163	169	166	165	171	177	167

Comments

There has been a reduction in the number of women of child bearing age taking Epilim, since 2010.

4.2 Number of children born to mothers taking sodium valproate

The number of live births where the mother was dispensed valproate during estimated duration of pregnancy by year of delivery is shown in Table 50.

Table 50: Number of live births to mothers taking Epilim in pregnancy

Year of birth	Live Births
2007	124
2008	116
2009	103
2010	58
2011	86
2012	73
2013	56
2014	47
2015	51
2016	36

Source: Ministry of Health Pharmaceutical Collection, extracted June 2017, ref: 2016-2644

Please note that reporting on valproate dispensing during pregnancy requires an NHI number to be recorded on the pharmaceutical dispensing. Before 2007, NHI reporting was infrequent, therefore data before this time has not been provided.

Data is only provided for dispensings of PHARMAC subsidised community pharmaceuticals. Birth data for 2016 is provisional and subject to change. Still births and births with pregnancy outcome not stated have been excluded.

Comments

There has been a reduction in the number of children born to mothers taking Epilim.

4.3 CARM data

To date, CARM have received 27 cases of Epilim exposure during pregnancy. [redacted] 7 cases described 26 pregnancies and 28 fetuses.

The daily dose taken by the mother was provided in 23 cases and ranged from [redacted] he first case was reported in 1978. In 19 cases, use of only one antiepileptic- sodium valproate was reported. In 7 cases, sodium valproate was taken with other anti-epileptics.

Congenital malformations (often coded as fetal valproate syndrome) were reported in 24 fetuses. Behavioural/neurodevelopmental problems were reported for 13 children. Death was reported as the outcome for five fetuses/infants. A full line listing is at Annex 2.

4.4 Risk minimisation and education

Healthcare professionals were informed in clinical services letter 165 in 1977 that prescribing of Epilim had been restricted 'based on the desire for further long-term clinical data and in particular, the possible dangers of a link between sodium valproate and teratogenicity in humans'.

In clinical services letter 216 in 1983 it was stated regarding valproate 'Attention is drawn to recent reports of spina bifida occurring in 1 percent of foetuses exposed to sodium valproate during pregnancy.'

More recently a *Prescriber Update* article was published in 2009 on the risk of congenital abnormalities with all anti-epileptics. An article specific to Epilim was published in 2013 with a follow up alert communication in 2014 (see summary on page 1).

The company made their additional educational materials available in New Zealand in 2014, a link was included in the alert communication.

The packaging also includes the written warning outlined above and the pictogram described above will also be added.

In addition, Medsafe has been working with other agencies in an ACC-led project to create information booklets for healthcare professionals and consumers outlining the risks of all anti-epileptic medicines in pregnancy (Annex 3).

5.0 DISCUSSION AND CONCLUSIONS

A referral is ongoing in the EU with the intention of determining whether the risk minimisation activities initiate after the last referral are working. Therefore, Medsafe used this opportunity to assess the situation in New Zealand.

The risk of teratogenicity caused by exposure to Epilim *in ut*ero was suspected when this medicine was first approved for use. This risk was confirmed in the early 1980's. In the early 2000's it also started to become clear that exposure to Epilim *in utero* also affected cognitive development.

It should also be noted that there appears to be a dose-effect relationship and that other anti-epileptics may also cause congenital malformations. There also appears to be an interaction between Epilim exposure and genetic factors and other environmental factors. Although folic acid supplementation has not been shown to be effective at reducing the risk of congenital malformations in most cases this was initiated too late to be effective.

A number of risk minimising activities have been undertaken in New Zealand: *Prescriber Update* articles, alert communication, provision of additional educational materials by the company and the inclusion of a warning on the packaging for Epilim.

The pregnancy contraindication was included in the Epilim data sheet in 2005 and there are extensive warnings relating to pregnancy and treatment advice as noted in section 2.3.

The data on use in women of child bearing age and the number of exposed pregnancies in New Zealand indicates that there has been a reduction in use in this population. The rate of decrease in exposure may be limited by access to specialist services to supervise changes in treatment. It is debatable whether the number of exposed pregnancies can be ever be reduced to zero, since there are women with epilepsy for whom there are no other effective treatments. However, for other indications this may not be the case. Certainly the French regulator is of the opinion that Epilim can be avoided in pregnancy in women with bipolar disorder. In this respect it should be noted that the current NZ indication for bipolar disease is much broader than the current EU indication. Compare:

Bipolar Disorder: For the treatment of manic episodes, maintenance and prophylactic treatment of bipolar disease.

With:

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

In addition the French have restricted the bipolar indication further to contraindicate use in women of child bearing potential not taking effective contraception. This may be adopted throughout the EU as a result of the referral.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- further regulatory action is required (eg, changes to the data sheet or indication)
- further communication is required.

7.0 ANNEXES

1. Full company report
2. CARM data
3. ACC booklets

8.0 REFERENCES

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